The Dissertation Committee for Hayley Jeanne Loblein Certifies that this is the approved version of the following Dissertation

Anxiety in Pediatric Epilepsy: The Role of Stigma and Illness Cognitions

Committee:

Timothy Keith, Supervisor

Jeffrey Titus, Co-Supervisor

Sarah Kate Bearman

Stephanie Cawthon

Anxiety in Pediatric Epilepsy:
The Role of Stigma and Illness Cognitions

by

Hayley Jeanne Loblein

Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

August 2019

Dedication

I would like to dedicate this manuscript to all of the parents and children who I have worked with during graduate school. I would particularly like to thank the families from the Pediatric Neuropsychology Clinic at Dell Children's Medical Center and the anxiety study at the Texas Child Study Center. You are the inspiration for my research. I hope that I can continue to engage in research that is meaningful and helpful to the families with whom I work.

Acknowledgements

First, I would like to thank my dissertation committee. Your contributions to my dissertation and my overall graduate school career are immeasurable. Dr. Titus, it's hard to put into words how much I appreciate your guidance and support over these past two years as a clinical and research supervisor. Thank you for the countless hours you have spent helping me find a way to merge my clinical and research interests. You have challenged me, laughed with me, and empowered me; I have walked away from every supervision energized and prepared to take on anything. I hope that one day I can be the type of mentor that you have been to me. Dr. Keith, thank you for your support from the first day of classes until my defense. I hope that one day I can lead in such a calm and reassuring way. Dr. Bearman, thank you so much for your advice and guidance through all aspects of my graduate school journey. I hope that one day I can be as dedicated as you are to promoting evidence-based practices. Dr. Cawthon, your enthusiasm and commitment to engaging students in their learning and research was palpable from when I first met you on interview day. I hope that one day I will be able to inspire and energize students in such an effective way.

I would also like to thank my cohort. Abigail, Ashlee, Becca, Danika, Duncan, and Josh, you've kept me sane through every graduate school hurdle. I'm so lucky to have met such a wonderful group of people who will be life-long friends and colleagues.

Finally, I would like to thank my family. Mom, Dad, Chaz, and Chelsea, your support and encouragement have always inspired me to achieve more. And to Brandon, my partner, thank you for moving to Austin to support me in graduate school and for reminding me to laugh along the way.

Abstract

Anxiety in Pediatric Epilepsy: The Role of Stigma and Illness Cognitions

Hayley Jeanne Loblein, Ph.D.

The University of Texas at Austin, 2019

Supervisors: Timothy Keith & Jeffrey Titus

Youth with epilepsy are at an increased risk for developing anxiety when compared to healthy youth (Alwash, Hussein, & Matloub, 2000; Jones et al., 2007; Russ et al., 2012) and when compared to youth with other chronic health conditions (Pinquart & Shen, 2011). Parents have become a significant focus of research examining the environmental risk and protective factors for anxiety in healthy children (Creswell, Murray, & Cooper, 2011; Gregory & Eley, 2007), and this is an area of growing research in youth with epilepsy (Jones & Reilly, 2016; Rodenburg, Meijer, Dekovic, & Aldenkamp, 2006; Schraegle & Titus, 2017a). The following study aimed to examine the medical and psychosocial risk factors for anxiety in youth with epilepsy.

Participants included 121 children and adolescents with epilepsy at a tertiary outpatient clinic in Central Texas who were referred by their neurologists for a neuropsychological evaluation to assist with treatment planning. Parent perceptions of stigma and parent illness cognitions were examined to determine their relationship with parent report of anxiety, seizure-related variables, and parent history of psychopathology.

Using multiple regression, parent perceptions of stigma were a statistically significant predictor of parent reported child anxiety. Additional moderation analysis suggested that there is an interaction between parent perceptions of stigma and seizure severity; at higher levels of seizure severity, higher parent perceptions of stigma were related to higher parent reported features of anxiety. This suggests the potential for parent perceptions of stigma to play an important role in anxiety in pediatric epilepsy, particularly in the context of high seizure severity. Additionally, parent perceptions of stigma, parent illness cognitions, and parent reported child anxiety were all related to parent reported quality of life, suggesting the importance of addressing these psychosocial factors to improve quality of life in youth with epilepsy.

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Chapter 1: Introduction

Epilepsy is a neurological disorder characterized by a predisposition to generate seizures (Fisher et al., 2014). Approximately 1% of children are diagnosed with epilepsy, making it the most common chronic neurologic condition in childhood (Aaberg et al., 2017; P. R. Camfield & Camfield, 2015; Russ et al., 2012). Epilepsy places a considerable burden on society and in the United States the economic burden of epilepsy is estimated to be 9.6 to 12.5 billion dollars annually (Begley et al., 2000; Institute of Medicine, 2012; Yoon, Frick, Carr, & Austin, 2009). The etiology of epilepsy is diverse and includes structural, genetic, infectious, metabolic, immune, and unknown causes. While seizures are the defining feature of epilepsy, the cognitive, social, and emotional burden that can be associated with the underlying brain dysfunction can have a significant impact on quality of life in youth with epilepsy (Fisher et al., 2014).

Epilepsy is considered a disease of brain networks, wherein seizures are just one symptom of brain dysfunction (Smith, 2016). Youth with epilepsy are at increased risk for cognitive difficulties because of underlying brain dysfunction and due to the effects of seizures and AEDs on developing brains (Institute of Medicine, 2012). There is a greater risk for negative psychosocial outcomes in epilepsy, such as lower social competence, more school problems, and limited activity when compared to healthy children (Russ et al., 2012). Epilepsy affects social functioning by limiting an individual's participation in activities and restricting their independence (Institute of Medicine, 2012).

When compared to healthy children or youth with other chronic health conditions, youth with epilepsy are at an increased risk for a variety of psychopathologies, including anxiety, depression, attention-deficit/hyperactivity disorder, and autism (Austin et al., 2011; Caplan et al., 2005; Dunn, Austin, & Perkins, 2009; Reilly, Kent, & Neville, 2013). Seizure related variables (e.g., high seizure frequency, poor seizure control, and multiple anti-epileptic medications [AEDs]) and psychosocial factors (e.g., stigma, coping, and family functioning) are implicated in the increased risk of psychopathology in youth with epilepsy (Caplan et al., 2004; Dunn & Austin, 2004; Reilly et al., 2013).

Youth with epilepsy are at a markedly increased risk for developing anxiety when compared to healthy controls (Alwash, Hussein, & Matloub, 2000; Jones et al., 2007; Russ et al., 2012) and when compared to youth with other chronic health conditions (Pinquart & Shen, 2011). However, despite its prevalence, anxiety has been referred to as the "forgotten" disorder in epilepsy because it has been widely ignored in the epilepsy literature (Gandy et al., 2015). The etiology of anxiety in pediatric epilepsy appears to be multifactorial and likely involves a variety of biological, psychosocial, and familial risk and protective factors (Jones et al., 2015).

There is emerging evidence that anxiety and epilepsy have a bidirectional relationship, as features of anxiety occasionally precede the onset of seizures, suggesting a common underlying biological vulnerability (Adelöw, Andersson, Ahlbom, & Tomson, 2012; Jones et al., 2007; Kanner, 2009). Higher symptoms of anxiety in youth with epilepsy may be related to dysfunction within the limbic system and/or neurotransmitter

pathways that create vulnerabilities to internalizing psychopathology. Higher symptoms of anxiety in youth with epilepsy may also be attributable to seizure-related variables, such as taking more than one AED (i.e., polytherapy), high seizure frequency, or poor seizure control (Reilly et al., 2013).

There are also a variety of psychosocial variables that are unique to youth with epilepsy that make them more vulnerable to anxiety. Children with epilepsy are often confronted with the unpredictable nature of seizures, which while anxiety provoking on its own, can be compounded by reduced control of the environment and parental overprotectiveness (Pinquart & Shen, 2011). Youth with epilepsy may also experience social anxiety because of the increased risk for peer rejection and victimization and the social stigma of epilepsy (Davies, Heyman, & Goodman, 2003; Pinquart & Shen, 2011). These psychosocial complications create a difficult social and family environment that includes elevated stress, restriction of activities, and isolation (Ellis, Upton, & Thompson, 2000).

Parents have become a significant focus of research examining the environmental risk and protective factors for anxiety in healthy children (Creswell et al., 2011; Gregory & Eley, 2007), and this is an area of budding research in youth with epilepsy as well (Jones & Reilly, 2016; Rodenburg, Meijer, Dekovic, & Aldenkamp, 2006; Schraegle & Titus, 2017a). Recent research has demonstrated that parent history of psychopathology is related to anxiety in youth with epilepsy (Adewuya & Ola, 2005; Jones & Reilly, 2016; Schraegle & Titus, 2017a), and parent rejection is related to more internalizing problems (Rodenburg

et al., 2006). Conversely, positive parent-child relationships have been found to be related to lower internalizing symptoms (Rodenburg et al., 2006). Research regarding parent factors that influence anxiety in youth with epilepsy is emerging but remains limited, and significant work is needed to match the understanding of factors that impact the development of anxiety in children (Murray, Creswell, & Cooper, 2009).

Anxiety has important implications for the quality of life in youth with epilepsy. In the general population, individuals with anxiety report lower quality of life, and successful treatment of anxiety is associated with improvements in quality of life (Hofmann, Wu, & Boettcher, 2014; Olatunji, Cisler, & Tolin, 2007). Research in youth with epilepsy suggests that internalizing symptoms have a more negative impact on quality of life than other demographic or epilepsy-related variables (Stevanovic, Jancic, & Lakic, 2011). However, more research is needed to elucidate the medical and psychosocial risk factors of anxiety to improve quality of life in youth with epilepsy (Scott, Sharpe, Hunt, & Gandy, 2017).

A recent International League Against Epilepsy Task Force report (Dunn et al., 2016) suggested that it is important to assess for reversible causes of anxiety in patients with epilepsy, and Ekinci et al. (2009) emphasized the importance of investigating family factors to identify opportunities for intervention and successful treatment that can improve health-related quality of life. Research grounded in theory is needed to provide greater insight into the risk and protective factors for anxiety, and while individuals with epilepsy experience high levels of stigma, research examining the relationship between stigma and anxiety in youth with epilepsy is severely limited. Additionally, parents provide a unique

and important context for the development of anxiety, and to date, no research has examined how parent illness cognitions may impact anxiety in youth with epilepsy. Similarly, while parental psychopathology is a known risk factor for anxiety in the general population, research on the genetic and environmental influences of anxiety in youth with epilepsy is sparse.

The proposed research study aims to examine the medical and psychosocial risk factors for anxiety in youth with epilepsy. Participants included children and adolescents with epilepsy at a tertiary outpatient clinic in Central Texas who were referred by their neurologists for a neuropsychological evaluation to assist with treatment planning. Parent perceptions of stigma and parent illness cognitions were examined to determine their relationship with parent reported features of anxiety, seizure-related variables, and parent history of psychopathology. Finally, this research reviews the impact of parent reported anxiety on health-related quality of life in youth with epilepsy.

Chapter 2: Literature Review

This chapter will provide an overview of epilepsy, anxiety, and the current understanding of anxiety within pediatric epilepsy. It will begin with a description of epilepsy and its prevalence in youth and provide a brief overview of the etiology, classification, and treatment of epilepsy and will conclude with outcomes in pediatric epilepsy. Next, this review will provide a description of anxiety and its prevalence in youth, with an overview of the etiology of anxiety, associated risk and protective factors, treatment options, and outcomes for youth with anxiety. Finally, this review will describe the literature that examines the relationship between anxiety and epilepsy and the prevalence of anxiety symptoms in individuals with epilepsy. Various biological and environmental factors that place youth with epilepsy at greater risk for anxiety will be considered, along with a discussion of gaps in our understanding of anxiety within pediatric epilepsy. The chapter will conclude with the research questions and hypotheses related to how parent factors influence anxiety in youth with epilepsy.

Epilepsy

Epilepsy is a neurological condition characterized by the occurrence of unpredictable seizures (Institute of Medicine, 2012). An epileptic seizure is caused by neuronal activity in the brain that is abnormal and excessive; it is characterized by variable signs or symptoms dependent on the location of the neuronal activity (Fisher et al., 2014). It is important to note the distinction between epilepsy and seizures; seizures are the event,

while epilepsy is the disease associated with spontaneous and recurring seizures (Fisher et al., 2014). The Institute of Medicine (2012) considers epilepsy a spectrum of disorders that can vary in severity, type, and impact on individuals affected.

Incidence, prevalence, cost, and burden of pediatric epilepsy. Epilepsy is the most common chronic neurologic condition in childhood, affecting approximately 1% of children (Aaberg et al., 2017; P. R. Camfield & Camfield, 2015; Russ et al., 2012). An estimated 6.8 million people have been diagnosed with epilepsy and 5.7 million people have active epilepsy in developed countries (Ngugi, Bottomley, Kleinschmidt, Sander, & Newton, 2010). According to a recent Norwegian study, in the first ten years of life, approximately 1 out of every 150 children will be diagnosed with epilepsy (Aaberg et al., 2017). Incidence rates in children range from 41-187/100,000 (C. S. Camfield, Camfield, Gordon, Wirrell, & Dooley, 1996; P. R. Camfield & Camfield, 2015; Mung'ala-Odera et al., 2008). There is a higher incidence of epilepsy in the first year of life and in rural and underdeveloped countries (P. R. Camfield & Camfield, 2015). Researchers suggest that the incidence of epilepsy is declining in countries with higher incomes due to the reduced risk of infection and traumatic brain injury that cause epilepsy (Aaberg et al., 2017). The prevalence of epilepsy ranges from 3.2-6.7/1,000 children with a median prevalence of active pediatric epilepsy of 4.7/1,000 (P. R. Camfield & Camfield, 2015; Ngugi et al., 2010). The economic burden of epilepsy is estimated to be 9.6 to 12.5 billion dollars annually in the United States; this includes direct costs of hospitalizations and indirect costs of lost productivity (Begley et al., 2000; Institute of Medicine, 2012; Yoon et al., 2009).

Etiology. The etiology of epilepsy is diverse and includes structural, genetic, infectious, metabolic, immune, and unknown etiologies. Structural abnormalities of the brain that are visible on neuroimaging (e.g., lesions) may cause seizures, and typical causes of structural abnormalities include stroke, traumatic brain injury, infections, and malformations of cortical development (Scheffer et al., 2017). Infections (e.g., meningitis, encephalitis) are common and preventable risk factors for epilepsy (Vezzani et al., 2016). Certain genetic mutations (known or presumed), an array of metabolic disorders, and immune disorders may also cause epilepsy (Scheffer et al., 2017). While there are a multitude of etiologies of epilepsy, the cause of epilepsy is unknown in about 50% of children (P. R. Camfield & Camfield, 2015). An individual's epilepsy can have multiple etiologies, and each etiology has implications for treatment (Scheffer et al., 2017).

Diagnosis. According to the ILAE, epilepsy is diagnosed in one of three ways: (a) two or more unprovoked seizures that occur more than a day apart; (b) one unprovoked seizure with >60% probability of another seizure occurring in the next ten years; or (c) diagnosis of an epilepsy syndrome (Fisher et al., 2014). Unprovoked seizures imply the "absence of a temporary or reversible factor" that lowers the threshold for seizures on an otherwise normal brain (Fisher et al, 2014). Examples of provoked seizures include seizures associated with concussion, fever, or alcohol withdrawal (Fisher et al, 2014).

Classification. Epilepsy classification is a complex process that can be based on a variety of factors. Clinicians classify seizures by finding familiar patterns in the signs and symptoms of the seizure and utilizing ancillary data such as electroencephalograms (EEGs)

and magnetic resonance imaging (MRIs) (Fisher, Cross, D'Souza, et al., 2017). Due to the lack of fundamental knowledge of seizures, it is difficult to classify seizures based on their pathophysiology; however, seizures may be classified in many ways, such as by the anatomic structures involved (e.g., frontal/temporal), the networks involved (e.g., neocortical, limbic), or the observable or treatment-related aspects of the seizures (e.g., behavioral semiology, EEG pattern, response to medication) (Fisher, Cross, D'Souza, et al., 2017). The ILAE provides a framework for understanding the classification of epilepsy by providing a multi-level classification system that involves classification of seizure type, epilepsy type, and syndrome, as well as identification of the etiology (see Figure 1) (Scheffer et al., 2017).

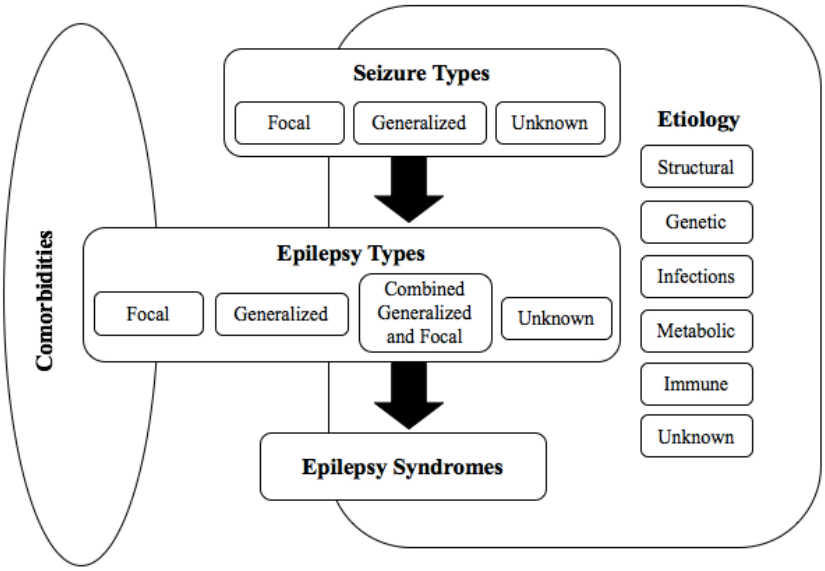

Figure 1: *Classification of epilepsy*. This figure illustrates the various levels of classification of epilepsy based on the ILAE framework. This figure is adapted from Scheffer et al. (2017).

The ILAE developed an operational system of classification of seizure type for use by clinicians that classifies seizures by location of onset and the signs and symptoms of the seizure (Fisher, Cross, D'Souza, et al., 2017). The next level of classification is for epilepsy type, which can include multiple seizure types. Epilepsy can also be classified based on the syndrome, which is defined as a cluster of features that occur together (Scheffer et al., 2017). The method of seizure classification utilized is dependent on the ultimate goal of classification. For the purposes of this dissertation, classification by seizure type and syndrome will be defined.

Seizure Type. According to the ILAE, classification by seizure type is a "useful grouping of seizure characteristics for purposes of communication" (Fisher, Cross, French, et al., 2017). The first step in classification of seizure type is to define the type of seizure onset (Fisher, Cross, D'Souza, et al., 2017). Focal and generalized seizures are the two main types of seizure onset, but seizure onset may also be unknown (Fisher, Cross, D'Souza, et al., 2017). Seizures are then classified based on whether they lead to a loss of awareness. Finally, seizures are classified based on the most prominent aspect of the seizure (Fisher, Cross, D'Souza, et al., 2017). The ILAE recommends that clinicians also provide additional descriptors that include sensations, emotions, and cognitions experienced during the seizure, movements of specific body parts, and laterality (Fisher, Cross, D'Souza, et al., 2017). See Figure 2 for visual representation of the classification of seizure types.

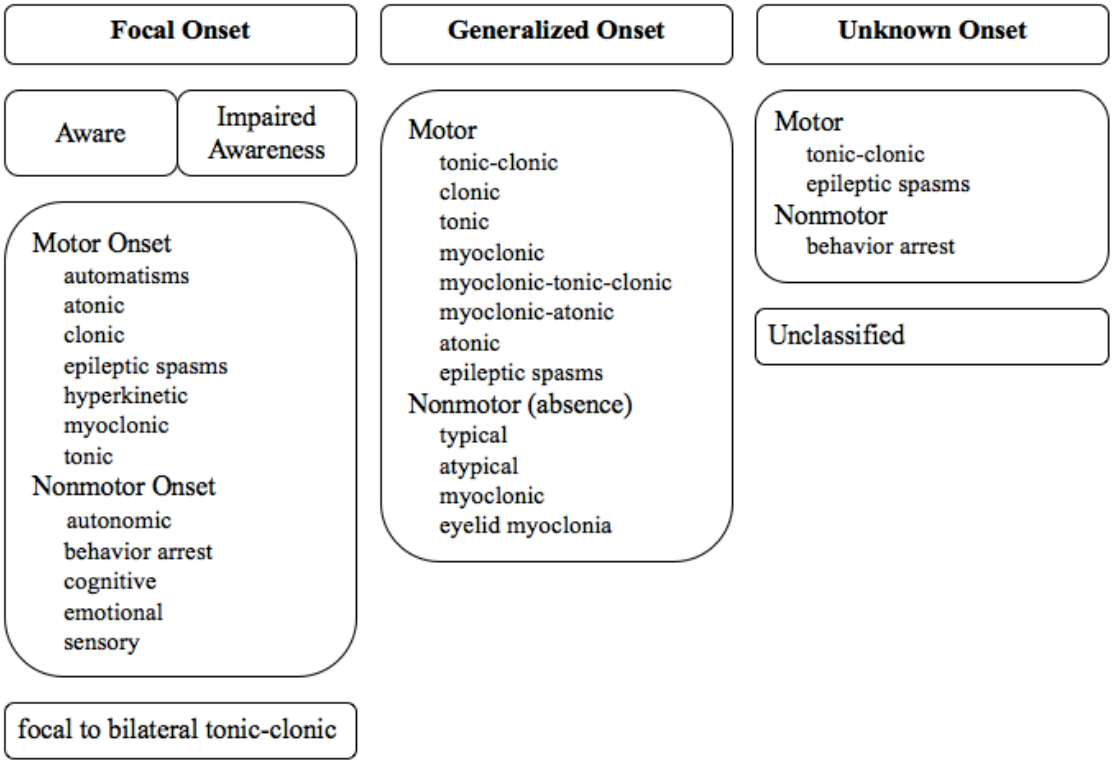

Figure 2: *Classification of seizure type*. This figure illustrates the most recent ILAE guidelines for classification of seizure type. This figure is adapted from Fisher, Cross, D'Souza, et al. (2017).

Seizures with a focal onset occur within one hemisphere; the onset can be subcortical, localized, or widely distributed (Fisher, Cross, D'Souza, et al., 2017). Focal seizures are then classified based on whether the individual is aware during the seizure (Fisher, Cross, D'Souza, et al., 2017). Focal seizures can be further characterized by the "first prominent sign or symptom" of the seizure, which can be motor (e.g., jerking, loss of muscle tone) or nonmotor (e.g., hallucination) (Fisher, Cross, D'Souza, et al., 2017).

Generalized seizures originate in a network of neurons that span bilaterally (Institute of Medicine, 2012). Generalized seizures are further characterized based on whether they are motor or nonmotor. Nonmotor generalized seizures are also known as absence seizures, which "present with a sudden cessation of activity and awareness" (Fisher, Cross, D'Souza, et al., 2017).

Syndromes. An epilepsy syndrome is "a complex of clinical features, signs, and symptoms that together define a distinctive, recognizable clinical disorder" (Berg et al., 2010). Epilepsy syndromes are characterized by typical age of onset, EEG findings, seizure types, and imaging features (Institute of Medicine, 2012; Scheffer et al., 2017). Classification by epilepsy syndrome provides information for medical treatment planning as well as prognosis.

Treatment of epilepsy. A variety of treatments and therapies are available to treat epilepsy, including medication, vagus nerve stimulation, surgery, and diet.

Medication. Anti-epileptic drugs (AEDs) are the initial treatment of choice for children with epilepsy; AEDs work through a variety of mechanisms (e.g., enhancing inhibitory neurotransmission or suppressing neuronal excitability) to prevent epileptic seizures (Ortinski & Meador, 2004; Schmitz, 2002). If a child is taking one medication it is considered monotherapy; approximately 46-61% of children achieve seizure freedom after receiving the appropriate medication (Arts et al., 2004; C. S. Camfield, Camfield, Gordon, & Dooley, 1997). Polytherapy, which is the use of more than one AED, may be needed to achieve seizure freedom, but is associated a higher risk of side effects (Bergin,

2003). Approximately 42% of children who receive a second AED achieve seizure freedom (Arts et al., 2004; C. S. Camfield et al., 1997). Generally, children remain on medication for two years, with a gradual withdrawal of medication; 70% of children remain seizure-free after medication withdrawal (Bergin, 2003).

When an individual's seizures cannot be controlled with medication, the epilepsy is defined as intractable (also described as refractory, drug resistant, or pharmacoresistant) (Kwan et al., 2010). An ILAE task force defined intractable epilepsy across two levels. Level 1 criteria determine whether the intervention leads to seizure freedom as well as whether there are adverse effects of the treatment (Kwan et al., 2010). The Level 2 definition of intractable epilepsy is "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve seizure freedom" (Kwan et al., 2010). A number of definitions have been applied to the term intractable epilepsy, leading to variable criteria and different results, but approximately 6-10% of children have intractable epilepsy (Arts et al., 2004; Berg et al., 2001). When AED therapy is ineffective, neurologists will consider adjunctive therapies, such as vagus nerve stimulation (Schmitz, 2002).

Vagus nerve stimulation. Vagus nerve stimulation (VNS) is a treatment that uses an implanted device to send electrical signals to the brain through the vagus nerve and can be used in individuals over the age of twelve (Andrews, 2010). VNS can reduce the frequency of seizures by about 50% in individuals with intractable epilepsy who are not surgical candidates (Morris et al., 2013). In a study of 347 children, approximately 43% of

children with a VNS had a reduction in seizures by over 50% and 6.7% were seizure free after two years with the implant (Orosz et al., 2014).

Surgery. Seizure control can also be achieved through surgical removal of epileptogenic brain tissue (Schmitz, 2002). Surgical intervention is generally considered after three years of intractable epilepsy and if the patient is a good surgical candidate (e.g., localized structural lesion) (Schmitz, 2002). According to a meta-analysis, approximately 27-66% of patients achieve seizure freedom after epilepsy surgery (Téllez-Zenteno, Dhar, & Wiebe, 2005).

Other treatments. Other treatment options for epilepsy include diet and behavioral treatment. The ketogenic diet is a high fat, low carbohydrate diet that has been effective in the treatment of certain epilepsy syndromes and conditions (Kossoff et al., 2009). The modified Atkins diet and the low glycemic index treatment are other dietary therapies that may also be useful in the treatment of intractable epilepsy (Kossoff et al., 2009). Behavioral strategies, such as relaxation, biofeedback, and self-control, have been described in the literature, but are poorly researched and limited in their effectiveness (Schmitz, 2002). While there are a variety of efficacious treatments for seizures, it is important to note that seizures are just one aspect of epilepsy.

Outcomes and quality of life in epilepsy. The ILAE Task Force conceptualizes epilepsy as "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, and social consequences of this condition" (Fisher et al., 2014). Seizure freedom, while important, does not necessarily

translate to improved quality of life. Epilepsy also impacts cognition, academic functioning, psychosocial functioning, and emotional functioning. "If epilepsy is a disease of brain networks and cognition and behavior are the primary functions of those networks, then epilepsy may be as much a disorder of cognition and behavior as it is of seizures, with cognitive and behavioral symptoms either predating seizures, or vice versa" (Smith, 2016). It is important to consider that cognitive, academic, psychosocial, behavioral, and emotional difficulties associated with epilepsy may be aspects of the epilepsy itself, rather than just comorbidities.

Cognitive functioning. Seizures, as well as medications for seizures, affect cognitive ability in individuals with epilepsy. Antiepileptic drugs change neuronal activity and can lead to cognitive side effects, particularly in individuals on polytherapy (Ortinski & Meador, 2004). Common side effects of AEDs include sedation, dizziness, and distractibility (Ortinski & Meador, 2004). AEDs also impact neurodevelopment; therefore children are at an increased risk for cognitive side effects of these medications (Bergin, 2003; Ortinski & Meador, 2004; Reuner, Kadish, Doering, Balke, & Schubert-Bast, 2016).

Epilepsy itself is also a risk factor for cognitive difficulties. In a meta-analysis of cognitive functioning in idiopathic generalized epilepsy (IGE), researchers found that individuals with IGE had significantly lower scores across all cognitive domains, except for visual-spatial abilities, when compared to healthy controls (Loughman, Bowden, & D'Souza, 2014). Loughman and colleagues (2014) also found that approximately 25% of individuals with IGE had an intellectual disability or borderline cognitive difficulties.

Children with epilepsy are at considerable risk for cognitive difficulties because their brains are still developing (Institute of Medicine, 2012). Reuner et al. (2016) found that children with new-onset epilepsy had impaired cognitive performance compared to healthy controls, even before starting medication therapy. Furthermore, they found that children with chronic epilepsy had even poorer cognitive performance than children with new onset epilepsy. Several seizure and brain-related factors, such as earlier onset of seizures, cerebral lesions, and seizure severity, frequency, type, and duration are related to cognitive functioning in individuals with epilepsy (Ortinski & Meador, 2004). Seizure control and cognitive functioning are important outcomes to consider because chronic intractable epilepsy and low intelligence are risk factors for poor psychosocial functioning in individuals with epilepsy (Geerlings et al., 2015).

Psychosocial functioning. Children with epilepsy are at greater risk for negative psychosocial outcomes compared to children without seizures. Epilepsy may affect the ability to function independently and participate in social activities (Institute of Medicine, 2012). Adolescents may be particularly affected because epilepsy is associated with a loss of independence and individuals with epilepsy are unable to drive. In a report from the National Survey of Children's Health, researchers found that children with epilepsy were more likely to have low social competence, school problems, and limited activity when compared to children who were not diagnosed with epilepsy (Russ et al., 2012). Epilepsy also has psychosocial consequences that extend into adulthood. In a study of adults with epilepsy in the Netherlands, researchers found that having epilepsy affects employment,

marital status, learning achievement, and independence (Shackleton, Kasteleijn-Nolst Trenite, de Craen, Vandenbroucke, & Westendorp, 2003). Individuals with epilepsy might also experience difficulty with interpersonal relationships due to their experiences of perceived stigma (McCagh, Fisk, & Baker, 2009).

Epilepsy can cause psychosocial difficulties for the whole family of an individual with epilepsy; this includes stress, restriction of activities, and stigmatization (Ellis et al., 2000). In a study of 138 young adults with epilepsy, researchers found that poor family support was a strong predictor of poor psychosocial outcomes (Geerlings et al., 2015). It is important to understand and address family and psychosocial functioning to improve quality of life in individuals with epilepsy.

Stigma. Individuals with epilepsy are at an increased risk of feeling stigmatized and discriminated against because of their epilepsy (Baker, Brooks, Buck, & Jacoby, 2000). Stigma is the experience of feeling discredited because an individual is different or undesirable to others in society (Goffman, 1968). Stigma can be experienced internally (e.g., feelings, thoughts, and beliefs about the self), interpersonally (e.g., interactions with others), and institutionally (e.g., differential treatment in society) (Muhlbauer, 2002). Health-related stigma can be defined as "a social process or related personal experience characterized by exclusion, rejection, blame, or devaluation that results from experience or reasonable anticipation of an adverse social judgment about a person or group identified with a particular health problem" (Weiss & Ramakrishna, 2006). Theoretical models of stigma suggest six dimensions of stigma: concealability (e.g., visibility), course of the mark

(e.g., salience over time), disruptiveness, aesthetics (e.g., unattractiveness), origin (congenital, accidental, or intentional), and peril (e.g., danger to others) (E. E. Jones, 1984). Youth with epilepsy are particularly vulnerable to internalized perceptions of stigma. In a study of 174 youth with epilepsy, researchers found that child perceptions of stigma were related to greater need for information and support, greater child fear and worry about seizures, more severe seizures, and younger age (Austin, Perkins, & Dunn, 2014).

Psychopathology. Youth with epilepsy are at increased risk for anxiety, depression, attention-deficit/hyperactivity disorder, and autism when compared to healthy controls and other youth with chronic illness (Austin et al., 2011; Caplan et al., 2005; Dunn et al., 2009; Reilly et al., 2013). In a large population-based study, neurodevelopmental spectrum disorders, including developmental delays, language problems, dyslexia, learning disorders, and autism spectrum disorder were found in 41.7% of children with epilepsy (Berg, Caplan, & Hesdorffer, 2011). In another population-based study, 21% of children with epilepsy met criteria for autism (Reilly et al., 2014). Reilly and colleagues (2014) found that 33% of children with epilepsy met criteria for ADHD. Children with epilepsy are also reported to have more behavior problems than their siblings (11.3% compared to 4.6%) (Austin et al., 2011).

Rates of anxiety and depression are also elevated in children with epilepsy, with prevalence in population-based studies ranging from 5% to 24% in anxiety and 7% to 13.4% in depression (Berg et al., 2011; McDermott, Mani, & Krishnawami, 1995; Reilly et al., 2014). In a meta-analysis, researchers found large effect sizes (d=1.27) for parent

reported internalizing problems when comparing children with epilepsy and normative controls (Rodenburg, Stams, Meijer, Aldenkamp, & Dekovic, 2005). In a population study of over 10,000 children, which included 67 children with epilepsy and 47 children with diabetes, researchers found that the rate of "emotional" psychiatric disorders in individuals with epilepsy was about 16%, compared to 6.4% in children with diabetes and 4.2% in the control group (Davies et al., 2003).

A bidirectional relationship may exist between mood/anxiety disorders and epilepsy (Kanner, 2009). Jones et al. (2007) found that forty-five percent of children with idiopathic epilepsy had an onset of a psychiatric disorder prior to their first seizure. Additionally, the higher prevalence of psychopathology and cognitive and linguistic impairments in children with epilepsy suggests that there is a common underlying neuropathology (Austin & Caplan, 2007). Berg and colleagues (2011) demonstrated that individuals with "complicated" epilepsy have more neurodevelopmental and psychiatric disorders than those with uncomplicated epilepsy. High seizure frequency, poor seizure control, and polytherapy are all associated with greater risk for psychopathology in pediatric epilepsy (Reilly et al., 2013). Other seizure variables, including seizure type, age of onset, and duration, are not consistently associated with psychopathology (Reilly et al., 2013). While factors related to epilepsy are associated with higher levels of psychiatric problems in children and adolescents with epilepsy, psychosocial factors may also affect psychopathology in children with epilepsy (Caplan et al., 2004; Dunn & Austin, 2004). Despite the high prevalence of psychiatric symptoms in pediatric epilepsy only one third

of youth with epilepsy and mental health conditions are diagnosed (Reilly et al., 2014), and only 33% of youth with epilepsy with affective and anxiety disorders actually receive mental health treatment (Caplan et al., 2005).

Quality of life. While seizure control is important, the focus of research in epilepsy has shifted to consider implications for quality of life. Quality of life is an "individuals' perceptions of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" ("WHO | WHOQOL," n.d.). In a study that examined the trajectories of health-related quality of life in 120 children with newly diagnosed epilepsy, Loiselle and colleagues (2016) found that 42% of children were at risk for low quality of life. Several variables have been associated with quality of life in youth with epilepsy, including seizure related variables (number of AEDs, AED side effects, seizure frequency), cognitive impairment, internalizing symptoms, socioeconomic status, and family functioning (Conway et al., 2016; Loiselle, Ramsey, Rausch, & Modi, 2016; Reilly, Atkinson, Das, et al., 2015b).

Anxiety

Anxiety is the most common mental health disorder that affects children and adolescents (Rockhill et al., 2010). Anxiety is the emotional reaction precipitating from the anticipation of a real or imagined threat to the self or others (Fonseca & Perrin, 2011). It is a "future-oriented emotion, characterized by perceptions of uncontrollability and unpredictability over potentially aversive events and a rapid shift in attention to the focus of potentially dangerous events or one's own affective response to these events" (Barlow,

2002). While fear and anxiety of certain situations are normative and developmentally appropriate, anxiety disorders are characterized by fear that is excessive or persistent beyond a developmentally appropriate time period (American Psychiatric Association [APA], 2013).

Lang (1968) described three main components to anxiety: a motor response, a subjective/cognitive response, and a physiological response. The motor response is characterized by behaviors, such as restlessness, immobility, and distress, activated to avoid or escape the anxiety provoking stimulus (Lang, 1968). Worries and fearful anticipation characterize the cognitive response to anxiety, while the physiological response to anxiety consists of the somatic symptoms associated with high autonomic arousal, such as increased heart rate and sweating (Lang, 1968).

The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) reflects this three-part model of anxiety in its definitions of the various anxiety disorders (American Psychiatric Association [APA], 2013). There are several different types of anxiety disorders that can be distinguished from each other by the cognitive ideations (thoughts and beliefs) as well as the situations or objects that are feared or avoided (APA, 2013). Children with separation anxiety have fears or worries that something harmful will happen to attachment figures or something will happen that will separate them from an attachment figure (APA, 2013). Youth with separation anxiety are typically "clingy" and may cry or become upset when separated from an attachment figure, be reluctant or refuse to go to school, be afraid to be alone, have stomach aches or other physical symptoms when

separated from attachment figures, or have nightmares about separation (Vasey, Bosmans, & Ollendick, 2014). Children with selective mutism may have a fear of and avoid speaking in certain situations where it is expected (e.g., in school), but are capable of talking in other situations (e.g., around family) (APA, 2013). Specific phobias are characterized by fear of certain, specific things, such as animals, blood, or other things in the environment. Children with specific phobias may cry, freeze up, or cling to an attachment figure when near these feared objects or situations (APA, 2013). Individuals with social anxiety have a fear of embarrassing themselves or being judged by others and avoid social interactions and social situations (APA, 2013). Panic disorder is characterized by a worry about having panic attacks, which consist of feelings of intense fear or discomfort that are associated with somatic symptoms and catastrophic thoughts (APA, 2013; Vasey et al., 2014). Agoraphobia is defined as a fear of the inability to escape from certain public environments, such as in a crowd (APA, 2013). Individuals with generalized anxiety have persistent, excessive, and uncontrollable worry about many different types of things, such as performance or perfectionism, and they typically have physical symptoms that accompany this worry such as restlessness, muscle tension, concentration problems, and difficulty sleeping (APA, 2013; Vasey et al., 2014).

Childhood through adolescence is considered a key risk period for the first symptoms of anxiety (Beesdo-Baum & Knappe, 2012). During development, many different types of fears and anxieties are typical and it can be challenging to distinguish between normative fears, mild symptoms of fear and anxiety, and anxiety disorders

(Beesdo-Baum & Knappe, 2012). The fears of children evolve as they develop; typical fears of early childhood are characterized by concrete and immediate threats and, as children get older, fears evolve to anticipatory and more abstract or imagined fears (Beesdo-Baum & Knappe, 2012). An anxiety disorder may develop when anxiety symptoms persist, are more intense than expected for a child's development or out of proportion from the threat posed, and cause impairments in important areas functioning, such as school or social functioning (Craske & Stein, 2016).

Prevalence. Anxiety is the most prevalent mental health disorder and affects one in nine people worldwide (Craske & Stein, 2016). Estimates of the prevalence of anxiety in children vary due to multiple factors, including age groups included, assessment instruments, informant, and diagnostic categories used (Beesdo-Baum & Knappe, 2012). Despite this difficulty, a recent meta-analysis estimates a world-wide prevalence rate of anxiety in children and adolescents of 6.5%, affecting approximately 117 million youth (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). Prevalence rates in an additional meta-analysis suggests a prevalence of 10.2% (Costello, Egger, & Angold, 2005). Lifetime prevalence rates of anxiety are as high as 31.9% (Merikangas et al., 2010). The economic burden of anxiety was estimated to be approximately $43 billion annually in the United States in the 1990s; this includes costs associated with treatment, loss of productivity, and mortality (Greenberg et al., 1999).

Diagnosis. Anxiety is typically diagnosed in children through diagnostic interviews and rating scales. Semi-structured interviews utilize criteria from diagnostic systems, such

as the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), to determine whether children meet certain criteria for a diagnosis. Semi-structured interviews provide in-depth insight regarding the specific types of anxiety the child is experiencing and are helpful with treatment planning. Clinical judgment is needed to determine the interference of the anxiety, which consists of determining the severity, frequency, persistence, and impairment of functioning (Craske & Stein, 2016). Diagnostic interviews can be time consuming and difficult to use to identify children at risk for anxiety. Furthermore, while diagnostic criteria are useful for clinicians working to treat anxiety in youth, Craske and Stein (2016) emphasize that anxiety is a dimensional construct.

Rating scales can be administered to different informants (such as parents, teachers, or the child) to quantify the amount, degree, or magnitude of anxiety symptoms (Silverman & Ollendick, 2005). Rating scales are useful in assessing and screening for anxiety in youth and are frequently utilized in research to identify and quantify features of anxiety (Silverman & Ollendick, 2005). Such scales are especially useful to identify maintaining variables for anxiety, as well as mediators and moderators for features of anxiety (Silverman & Ollendick, 2005). Despite the ease of use and utility of rating scales, social-desirability may lead to under-reporting of anxiety-symptoms on self-reported rating scales (Silverman & Ollendick, 2005). Additionally, it is important to note that rating scales represent a somewhat arbitrary metric, and could lead to false positives and/or false negatives (Silverman & Ollendick, 2005). Despite some of these challenges regarding the use of rating scales, Silverman and Ollendick (2005) suggest that measurement of anxiety

symptoms along a continuum allows researchers to identify degrees of disturbance and patterns of manifestations without categorizing children or presuming an underlying disease.

Risk and protective factors. Risk factors are defined as variables that influence, intensify, precipitate, maintain, or predispose to maladaptation or psychopathology (Vasey & Dadds, 2000). Complementary to this concept, protective factors "serve to protect against the development of childhood anxiety disorders or to foster a return to a normal developmental pathway subsequent to their onset" (p. 7, Vasey & Dadds, 2000). It is important to note that risk and protective factors can be enduring or transient, they are not merely additive but influence each other, and they may contribute to other psychopathologies. Vasey and Dadds (2000) outline a variety of predisposing factors that influence anxiety, including: genetics, neurobiology, temperament, emotion regulation, cognitive biases and distortions, parental responses, experiences with conditioned stimuli, and level of exposure to stimuli. Below is a brief summary of the various risk and protective factors that serve to maintain or ameliorate symptoms of anxiety.

Genetic influences. A genetic predisposition for anxiety is clear throughout the literature. Children of parents with anxiety are almost four times more likely to have anxiety than children of parents without anxiety (Micco et al., 2009). The genetic aspects of anxiety are elucidated through several avenues of research, including twin studies, association studies, linkage studies, and genome-wide association and linkage studies.

Several genes have been implicated in the expression of anxiety. Studies examining epigenetics highlight the importance of environmental factors on gene expression.

Studies of monozygotic and dizygotic twins provide information about how genes can influence anxiety because they parcel anxiety into three factors: additive genetic influences (e.g., gene alleles), shared environmental influences (e.g., parenting), and unshared environmental influences (Gregory & Eley, 2011). Heritability estimates for anxiety disorders are in the range of 30-40% (Hettema, Neale, & Kendler, 2001). Genetic influences also account for anxious behaviors, including behavioral inhibition, shyness, emotional dysregulation, and neuroticism (Barzman, Geise, & Lin, 2015; Battaglia et al., 2017; Bienvenu, Hettema, Neale, Prescott, & Kendler, 2007; Johnson, Carver, Joormann, & Cuccaro, 2016).

Several genes have been implicated in the expression of anxiety, many of which are associated with neurotransmitter systems. The serotonin transporter polymorphism (5-HHLPR) can vary in the number of repeated sections of DNA, and both longer and shorter alleles have been implicated in higher anxiety personality symptoms (Schinka, Busch, & Robichaux-Keene, 2004). Anxiety is linked to DNA changes that affect catechol-O-methyltransferase, an enzyme that is important for both serotonin and dopamine pathways, and the GAD1 gene, which synthesizes GABA from glutamate (Hettema et al., 2006; McGrath et al., 2004). Finally, genes for the corticotrophin-releasing hormone, which is released during fear, is associated with behavioral inhibition (Smoller et al., 2003).

Epigenetic changes are the alterations made in the chemical and physical structure of DNA induced by environmental factors (Higley, 2016). Epigenetics can elucidate how the environment affects gene expression. For example, in a study of rats, maternal care (e.g., licking and grooming) produces methylation of a glucocorticoid receptor promotor in the hippocampus associated with the stress response (Champagne et al., 2006). This provides evidence that biological changes may be induced by environmental factors. There are many genetic influences of anxiety, but studies reviewing epigenetics and aspects of gene expression further complicate our understanding about the heritability of anxiety and lay the groundwork for the importance of environmental factors. It is likely that genetic factors predispose children to a "vulnerability" for anxiety (Barlow, 2002).

Neurobiological influences. Neurobiological factors have been assessed to understand the development of anxiety in children. Many neurobiological influences, including brain structures, such as the amygdala, and neurotransmitter/endocrine systems have been associated with anxiety. The amygdala has been at the forefront of research on brain regions involved in fear and anxiety. It is an important component of the limbic system, which is involved in processing emotional experiences (Cummins & Ninan, 2002). Hyperactivation of the amygdala and insula was found in a meta-analysis of imaging studies of PTSD, social anxiety, and specific phobia; this hyperactivation was also found in healthy subjects undergoing fear conditioning (Etkin & Wager, 2007). In other fear conditioning paradigms, expression of the fear response has been associated with the dorsal anterior cingulate and medial prefrontal cortex (ACC/mPFC), while the inhibition or

extinction of these responses has been associated with the ventral ACC/mPFC (Etkin, Egner, & Kalisch, 2011). Etkin (2012) suggests that the ACC/mPFC are dysfunctional in individuals with anxiety.

Multiple endocrine systems and neurotransmitters have been implicated in anxiety; the neurotransmitters and systems involved may vary based on the anxiety disorder experienced. GABA, which is an inhibitory neurotransmitter, has been associated with stress and anxiety (Kalueff & Nutt, 2007). Individuals with GAD have reduced GABA-A receptor density and GABA-A agonists reduce symptoms of anxiety (Kalueff & Nutt, 2007; Martin, Ressler, Binder, & Nemeroff, 2009). Serotonin has also been implicated in anxiety, and some studies have determined that there is decreased 5HIAA CSF concentration in anxiety (Martin et al., 2009). The serotonin transporter is a protein that moves serotonin from the synaptic cleft to the presynaptic neuron and higher density has been correlated with more anxiety symptoms in GAD (Lesch et al., 1996; Martin et al., 2009). 5HT1A has been shown to increase anxiety at hippocampal postsynaptic receptors and decrease anxiety at dorsal raphe nucleus autoreceptors (Martin et al., 2009). Finally, the 5HT2 neurotransmitters increase anxiety symptoms and 5HT2 antagonists reduce anxiety symptoms (Martin et al., 2009; Vaswani, Linda, & Ramesh, 2003).

Temperament. Temperament is the socioemotional behavior seen in early development that shapes a child's mood and behavior in certain contexts (Pérez-Edgar & Fox, 2005). Behavioral inhibition, negative affect, harm avoidance, and novelty seeking are all temperaments that have been associated with symptoms of anxiety (Pérez-Edgar &

Fox, 2005). Temperament is thought to affect anxiety in four ways. First, in conjunction with the diathesis-stress model, temperament may interact with environmental stressors to predispose youth to anxiety (Vasey et al., 2014). The pathoplasticity model suggests that a child's temperament may also affect how parents or others interact with them, which shapes their environment (Vasey et al., 2014). Next, changes in temperament may be a product of the development of the anxiety disorder, which is known as the complication or scar model (Vasey et al., 2014). Finally, the continuity model suggests that temperament and anxiety have the same underlying processes and reflect the same construct (Vasey et al., 2014).

Behavioral inhibition is the tendency to be shy and cautious, which is a temperament that has been associated with anxiety (Hirshfeld et al., 1992; Kagan, Reznick, & Snidman, 1987; Kagan & Snidman, 1999). Children with behavioral inhibition are likely to be highly reactive to unfamiliar situations, which constrains the probability that the child will be uninhibited in his or her behavior (Kagan & Snidman, 1999). Behaviorally inhibited children have more physiological reactions to anxiety (e.g., increased heart rate, higher cortisol) and are more likely to experience anxiety (Hirshfeld et al., 1992; Kagan & Snidman, 1999). Having a behaviorally inhibited temperament is associated with physiological aspects of anxiety and shapes avoidance behavior of anxiety provoking environments.

Negative affect is characterized by the experience of negative emotions, high subjective distress, and displeasurable association with the environment (Lonigan, Phillips,

& Hooe, 2003). Negative affect is a component of the tripartite model of anxiety and depression, and high levels of negative affect are associated with anxiety in adolescents (Lonigan et al., 2003). In a meta-analysis of studies examining temperament in panic disorder, social anxiety disorder, and obsessive-compulsive disorder (OCD), researchers found that harm avoidance was positively associated with symptoms of all three diagnoses and there was a marginal negative relationship between novelty seeking and social anxiety and OCD (Kampman, Viikki, Järventausta, & Leinonen, 2014). It is important to note that while temperament has been associated with the development of anxiety, a child is both the producer of and a product of their environment because children develop through a reciprocal interaction with the environment (Pérez-Edgar & Fox, 2005).

Gender. Women are more likely than men to be diagnosed with an anxiety disorder; by the age of six, girls are two times more likely to have experienced anxiety (Costello et al., 2005; Craske & Stein, 2016; Lewinsohn, Gotlib, Lewinsohn, Seeley, & Allen, 1998). In a large sample of adults, researchers found that not only was anxiety more prevalent in women, but it was also more disabling and resulted in greater illness burden (McLean, Asnaani, Litz, & Hofmann, 2011). Despite the greater prevalence of anxiety in women and girls, it is still unclear why they are at greater risk for anxiety (Costello et al., 2005; Craske & Stein, 2016). When adjusted for potentially cofounding factors, anxiety is still more prevalent in girls (Lewinsohn et al., 1998).

Cognition, control, and learning. Information processing biases, composed of attention, interpretation, and memory biases, are cognitive distortions that are associated

with anxiety (Muris & Field, 2008). These cognitive distortions can be explained by the cognitive-behavioral theory of child psychopathology that suggests that anxiety results from schemas regarding danger and vulnerability that lead children to focus on threatening information and ultimately develop maladaptive thought patterns that maintain anxiety (Kendall, 1985). While anxiety and cognitions are inter-related, it is important to note that this does not necessarily imply a causal relationship; additionally, both environmental factors, such as learning, and genetic factors play a role in the development of cognitive distortions (Muris & Field, 2008).

Attention bias is the tendency to be hyper-attentive towards threatening information and is generally measured through Stroop tasks with emotionally laden words and dot-probe tasks (Muris & Field, 2008). A meta-analysis concluded that anxious children and adults demonstrate threat-related biases when compared to healthy controls (Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007). Youth with anxiety consistently demonstrate interpretation bias, which is the tendency to perceive ambiguous situations as threatening (Miers, Blöte, Bögels, & Westenberg, 2008; Muris & Field, 2008; Rozenman, Amir, & Weersing, 2014). Finally, a tendency to recall memories congruent with anxious cognitions is considered memory bias; however, evidence for this type of bias is lacking in studies of youth and adults with anxiety (Muris & Field, 2008). While there is evidence that children and adolescents demonstrate information processing biases, it is important to consider that developmental level will affect a child's ability to demonstrate

and verbalize cognitive distortions (Cartwright-Hatton, Reynolds, & Wilson, 2011; Muris & Field, 2008).

Researchers suggest that experience with uncontrollable events may predispose a child to a psychological vulnerability that leads them to perceive events as outside of their control (Chorpita & Barlow, 1998). Chorpita and Barlow (1998) propose that in early development, such uncontrollable events lead to a psychological vulnerability that is a mediator to anxiety, while later in development, the psychological vulnerability amplifies anxiety and acts as a moderator. In a recent meta-analysis, researchers found a mean effect size of -.524 between perceived control and anxiety; this relationship was stronger in adults than children (Gallagher, Bentley, & Barlow, 2014).

Learning also plays a key role in the development of anxiety. Rachman (1977, 1991) proposed three pathways for the acquisition of fear: conditioning, modeling or vicarious learning, and verbal acquisition. In other words, children may acquire fear through direct experiences, through observation of the reactions of others, through verbal information, or through a combination of all three (Field & Purkis, 2011).

Family factors. Environmental factors play an important role in the development of anxiety, and parents have become a large focus of research examining environmental risk and protective factors for anxiety (Creswell et al., 2011; Gregory & Eley, 2007). Murray et al. (2009) describes three pathways in which parents can influence the development of anxiety. First, parents may socialize their child in a way that leads the child to perceive that they are unable to cope with the dangers of the world (Murray et al., 2009).

Next, a child may learn anxiety from an anxious parent who models or verbally mediates anxiety (Murray et al., 2009). Finally, Murray and colleagues (2009) suggest that parents may respond to a child's anxiety in ways that maintain or intensify anxiety (e.g., accommodation and avoidance of anxiety provoking situations). Several parenting factors likely play a role in the development of child anxiety, including parental beliefs, parenting styles, and parenting behaviors.

While some aspects of the intergenerational transmission of anxiety may be due to genetic factors, it is also likely that parental anxiety leads to certain environmental factors that make children more vulnerable to anxiety. One potential mediator of parent and child anxiety is parental beliefs. In a study of 103 youth with anxiety, researchers found that parental beliefs about anxiety mediated the relationship between parent and child anxiety (Francis & Chorpita, 2011). Parenting styles have also been examined. Craske (1999) suggested that while parenting styles may activate trait anxiety, parenting behaviors may lead to the development of an anxiety disorder.

Parental control, characterized by over-involvement in activities, routines, or emotional experience, has also been examined as a factor in child anxiety. Parental control may act by reducing a child's sense of control of the environment, which can lead to anxiety (Barlow, 2000; Becker, Ginsburg, Domingues, & Tein, 2010; Chorpita, Brown, & Barlow, 1998). In a meta-analysis of parenting and child anxiety, researchers found that child anxiety was more strongly associated with parental control than with parental rejection; parental autonomy granting and child anxiety had an average correlation of -0.42 (McLeod,

Wood, & Weisz, 2007). McLeod and colleagues (2007) found that parenting accounted for about 4% of the variance in child anxiety, which suggests that while parenting and family factors play a role in the development of anxiety, they likely interact with other factors, such as the child's age, biological vulnerability, and other life events (Creswell et al., 2011; Murray et al., 2009).

Developmental psychopathology model of anxiety. The developmental psychopathology model of anxiety posits the concept of multideterminism: there are a wide range of causal influences for the development of anxiety that are complex, dynamic, and interact with each other (Vasey & Dadds, 2000). Vasey and Dadds (2000) suggest that the risk and protective factors for anxiety interact and influence each other in a transactional manner. They also present the concepts of multifinality and equifinality. Multifinality posits that any risk or protective factor can lead to multiple outcomes; for example childhood maltreatment, punishment, parental psychopathology, low socioeconomic status, and harsh parenting are non-specific risk factors for all mental health disorders (Craske & Stein, 2016). Complimentary to this concept is that of equifinality, which states that there are multiple pathways to the same outcome (Vasey & Dadds, 2000).

Vasey and Dadds (2000) propose an integrative model of developmental psychopathology that suggests that cumulative risk for anxiety is created from a balance of the transactional influences of risk and protective factors. They also suggest that there are two pathways to anxiety: one in which there are clear precipitating events (e.g., conditioning or exposure to stressful events) and another in which symptoms of anxiety

gradually intensify over time (Vasey & Dadds, 2000). In addition to the risk and protective factors that influence the development of anxiety, Vasey and Dadds (2000) also highlight factors that contribute to the maintenance and intensification of anxiety. These factors include: avoidance, incompetence across different skill domains (e.g. academic, emotion-regulation, social), cognitive biases and distortions, punishment and failure, and responses by others that influence avoidance (e.g., overprotection) (Vasey & Dadds, 2000). They propose that temperament and developmental status can alter the degree to which these factors influence anxiety (Vasey & Dadds, 2000). Additionally, Vasey and Dadds (2000) suggest that "desistance" of anxiety can be promoted through opposite and complimentary factors (e.g., exposure, cognitive restructuring).

Treatment of anxiety. Anxiety disorders in children are commonly treated through therapy and medication. Cognitive behavioral therapy (CBT) is an effective treatment for anxiety disorders in youth that generally includes psychoeducation, cognitive restructuring, coping skills training, and graduated exposures (Compton et al., 2010). In a review of treatments for youth with anxiety, well-established treatments with strong empirical support included CBT with exposure, exposure-only, modeling, CBT with parents, and CBT with medication (Higa-McMillan, Francis, Rith-Najarian, & Chorpita, 2016). Common practice elements that are aspects of the most well-established treatments include: exposure (87.9%), cognitive techniques (53.9%), relaxation (53.9%), psychoeducation (42%), and modeling (33.9%) (Higa-McMillan et al., 2016). Therapy that included

exposure-based approaches had larger effect sizes, more durability, and more current support in the literature (Higa-McMillan et al., 2016).

Selective serotonin-reuptake inhibitors (SSRIs) are the most common medications prescribed to treat anxiety in youth; however, there is still limited research regarding the safety and durability of these medications in children (Compton et al., 2010). Walkup and colleagues (2008) compared treatment with CBT alone, sertraline alone, a combination of sertraline and CBT, and placebo in a large multicenter randomized study of 488 children and adolescents between the ages of 7 and 17. Researchers found that combination therapy of sertraline and CBT led to the most improvement in anxiety symptoms, with 80.7% of children on combination treatment being very much or much improved, compared to 59.7% with CBT alone, 54.9% with sertraline alone, and 23.7% with placebo (Walkup et al., 2008). These findings suggest that SSRIs and CBT are effective treatments, but a combination of medication and therapy leads to the most improvement in anxiety symptoms.

Quality of life in anxiety. Anxiety has significant effects on an individual's quality of life. Childhood anxiety not only predicts anxiety in adolescence and adulthood, but anxiety can also be a predictor of other mental health problems in adulthood (Rapee, Schniering, & Hudson, 2009). In a meta-analysis of 23 studies, researchers found that individuals with anxiety had overall poorer quality of life than control subjects (Olatunji et al., 2007). Additionally, individuals with anxiety are particularly affected across the mental health and social functioning domains (Olatunji et al., 2007). In a study of 310 children

with a variety of psychopathology, researchers found that children with anxiety were most affected in the emotional domain of quality of life (Bastiaansen, Koot, Ferdinand, & Verhulst, 2004). Effective treatment of anxiety with medication is associated with improvements in quality of life and greater anxiety symptom reduction is associated with better improvement in quality of life (Hofmann, Wu, Boettcher, & Sturm, 2014). Treatment with cognitive behavioral therapy is also associated with moderate improvements in quality of life, particularly in the physical and psychological domains (Hofmann, Wu, & Boettcher, 2014).

Anxiety in Pediatric Epilepsy

The forgotten disorder. The prevalence of anxiety in individuals with epilepsy appears to be elevated compared to rates of anxiety in the general population (Scott, Sharpe, Hunt, & Gandy, 2017). This higher prevalence may be driven by both biological and psychosocial factors. Many researchers have suggested that there is a bidirectional relationship between anxiety and epilepsy, which can be driven by the biological correlates of anxiety and epilepsy (Adelöw et al., 2012; Kanner, 2009). Additionally, there are multiple psychosocial impacts of epilepsy that may lead to worry, including the impact of epilepsy on independence, school functioning, and relationships (Scott et al., 2017). Despite these biological, psychosocial, and environmental risk factors for anxiety in individuals with epilepsy, anxiety is still considered the "forgotten" disorder and has been, until more recently, widely ignored in the epilepsy research (Gandy et al., 2015). Symptoms of anxiety may be particularly missed in pediatric patients with epilepsy

because children with anxiety may not be able to verbalize their feelings and may present with disruptive or irritable behaviors (Ettinger et al., 1998). Scott and colleagues (2017) emphasize the importance of more research to elucidate the medical and psychosocial risk factors of anxiety in epilepsy in order to improve quality of life.

Prevalence of anxiety in epilepsy. Rates of anxiety in children and adolescents with epilepsy range from 5% to 38.5% (Berg et al., 2011; Caplan et al., 2005; J. E. Jones et al., 2007; Kwong et al., 2016; Reilly, Atkinson, Chin, et al., 2015; Russ et al., 2012; Schraegle & Titus, 2017b, 2017a; Williams et al., 2003). Reasons for the discrepancies in rates of anxiety may be related to methodological differences. In a study of 501 children with epilepsy recruited from 16 pediatric neurologists in Connecticut, Berg et al. (2011) found low rates of anxiety (5%); however, this study relied on parents to indicate whether or not their children had a variety of different psychopathologies approximately 9 years after epilepsy diagnosis. In contrast, through the use of a diagnostic interview, Jones and colleagues (2007) found rates as high as 38.5% in a study that included 53 children with recent onset idiopathic epilepsy recruited from two pediatric neurology clinics in Wisconsin. In a recent meta-analysis studying prevalence of anxiety and depression in adults with epilepsy, Scott and colleagues (2017) found that prevalence rates of anxiety varied based on method of diagnosis. Prevalence of anxiety was 8.1% in studies that utilized clinician judgement compared to a prevalence rate of 26.9% in studies that utilized a structured clinical interview, suggesting that clinicians may underestimate the prevalence of anxiety in individuals with epilepsy (Scott et al., 2017).

Anxiety is much more prevalent in children with epilepsy compared to heathy children or children with other chronic health conditions (Russ et al., 2012). In a national survey of over 90,000 children, 17% of children with epilepsy/seizure disorders were reported by their parents to experience anxiety compared to just 3% of children without epilepsy (Russ et al., 2012). Jones and colleagues (2007) compared 53 children with recent onset idiopathic epilepsy and 50 healthy controls using a diagnostic interview (KSADS) and found that 35.8% of children with epilepsy had anxiety compared to 22% of healthy controls. Additionally, they found that 45% of children with epilepsy had an onset of a psychiatric diagnosis before their first seizure and one third of these diagnoses were anxiety (Jones et al., 2007). In a study of 101 adolescents with epilepsy in Jordan, the odds ratio for anxiety was 3.66 when compared to healthy controls (Alwash et al., 2000). In a meta-analysis of anxiety in children with chronic illness, researchers suggested that children with epilepsy are one of the groups with the highest risk for anxiety symptoms and found the effect size was significantly elevated (d=.34) (Pinquart & Shen, 2011). While anxiety is prevalent in youth with anxiety, relatively few children receive adequate treatment. Caplan and colleagues (2015) found that of children with affective or anxiety disorders and suicidal ideation, only 33% were receiving mental health services.

Prevalence of specific anxiety diagnoses. In an MRI study of children with recent-onset epilepsy, 12.5% had a diagnosis of specific phobia, 9.1% had a diagnosis of separation anxiety, 6.8% had a diagnosis of social anxiety, and 5.7% had a diagnosis of generalized anxiety (Jones et al., 2015). A recent meta-analysis of depression and anxiety

in adults with epilepsy found the pooled prevalence of generalized anxiety to be 10.2%, social phobia was 5.3%, agoraphobia was 2.8%, panic disorder was 2.6%, and specific phobia was 1.3% (Scott et al., 2017).

Risk and protective factors for anxiety in pediatric epilepsy. Pinquart and Shen (2011) offer a variety of reasons for why children with a chronic illness may experience anxiety, including: confrontation with dangerous stimuli (e.g., seizures), increased fear of death, reduced control of the environment, uncertainty of illness and symptoms, risk of peer rejection and associated social anxiety, parental over-protectiveness, and illness symptoms that are similar to anxiety symptoms.

The etiology of anxiety in pediatric epilepsy is multifactorial, and likely involves psychosocial, biological, and familial factors (Jones et al., 2015). Herman and colleagues (1988) suggest a multietiological framework that integrates four hypotheses to understand the greater prevalence of psychopathology in epilepsy. First, they suggest that there are biological variables that are related to the cause, course, or outcome of the epilepsy that also affect psychopathology (Hermann, Whitman, Hughes, Melyn, & Dell, 1988). Second, Herman and colleagues (1988) suggest that psychosocial factors, such as stigma, discrimination, and loss of social support, create stress that make individuals with epilepsy more susceptible to psychopathology. Next, epilepsy medications may provide some risk for psychopathology. Finally, demographic variables, such as age, education, sex, and race, may be important factors to consider. This multietiological framework continues to be used when considering the risk and protective factors for anxiety in epilepsy; however, the

framework has recently been expanded to include family factors, such as parenting, family functioning, and parental psychopathology.

Biological correlates of anxiety in epilepsy. There are several aspects of brain dysfunction in epilepsy that may contribute to higher symptoms of anxiety. Depending on the location affected, seizures themselves may cause anxiety symptoms in individuals with epilepsy. The limbic system, which includes the amygdala and the hippocampus, is a brain region that is highly related to both anxiety and epilepsy. Common dysfunction in neurotransmitter pathways may also contribute to the higher prevalence of anxiety in individuals with epilepsy. Finally, there is emerging evidence that anxiety and epilepsy have a bidirectional relationship.

Seizures. Seizures are defined by four distinct phases: pre-ictal, ictal, post-ictal, and inter-ictal. Symptoms of anxiety can occur during any aspect of the seizure experience: ictally, postictally, or interictally. The pre-ictal period is defined as the time immediately prior to the seizure. The ictal period, or ictus, is the period of time when the seizure is occurring. Anxiety can occur during the ictal period when a person experiences fear during a seizure; this can be especially prevalent in individuals with temporal lobe epilepsy when a seizure causes amygdala activation (Beyenburg, Mitchell, Schmidt, Elger, & Reuber, 2005). Seizures that propagate from other limbic structures, such as the orbitofrontal cortex or the cingulate gyrus, also can lead to ictal fear (Biraben et al., 2001). The post-ictal period is the time immediately after a seizure. Immediately after a seizure, individuals with epilepsy might be confused or disoriented, which can lead to anxious symptoms

(Beyenburg et al., 2005). The inter-ictal period is the time between seizures. Individuals with epilepsy might have symptoms of anxiety during the time between seizures for a number of reasons, including: phobia of seizures, problems with adjustment, side effects of medication, or surgical consequences (Beyenburg et al., 2005). Anxiety that occurs immediately before, during, or after the seizure is generally transitory; anxiety that occurs during the inter-ictal period will be the primary focus of this dissertation.

Prefrontal cortex. In an MRI study of 44 children with complex partial seizures, researchers found significantly smaller inferior frontal white matter volumes in children with a psychiatric diagnosis compared to those without (Daley et al., 2007). In a sample of 88 children with recent-onset epilepsy and 49 healthy controls, Jones and colleagues (2015) found that children with epilepsy and anxiety had significantly thinner cortex in the right frontal pole, right orbital frontal cortex, and left medial orbital frontal cortex. These studies suggest that the prefrontal cortex may develop differently in children with both epilepsy and anxiety.

Amygdala. The amygdala is at the forefront of research relating epilepsy and psychopathology. Emotional symptoms, such as fear and palpitations, may emerge when the amygdala is activated during a seizure (Yilmazer-Hanke, O'Loughlin, & McDermott, 2016). Researchers suggest that the amygdala may also be important to the inter-ictal experience of anxiety in epilepsy, particularly in patients with temporal lobe epilepsy (Yilmazer-Hanke et al., 2016). In an MRI study of 28 children with cryptogenic epilepsy and complex partial seizures (CPS), researchers found no significant differences in

amygdala volumes between the epilepsy and control group, but found that children in the CPS group with affective and anxiety disorders had greater asymmetry in the amygdala and significantly larger left amygdala volume compared to children without psychopathology (Daley et al., 2008). Jones and colleagues (2015) also found significantly larger left amygdala volume in children with epilepsy and anxiety. In a study of 26 children with absence epilepsy, Cohen (2009) found that amygdala volume was not related to an affective or anxiety disorder diagnosis and suggested that this may be related to the shorter duration of illness in children with epilepsy. Overall, there is some evidence that suggests that children with epilepsy are at risk for or may have differences in amygdala volume.

Neurotransmitters. Serotonin and the 5HT receptors have been consistently associated with symptoms of anxiety (Lesch et al., 1996; Martin et al., 2009; Vaswani et al., 2003) and research has shown that there are abnormalities in these receptors in individuals with temporal lobe epilepsy (Merlet et al., 2004; Savic et al., 2004; Toczek et al., 2003). In a study using PET imaging, individuals with temporal lobe epilepsy had reduced serotonin receptor binding in the area of seizure focus (Toczek et al., 2003). Other researchers have shown that the regions affected by reduced receptor binding expand to areas of the limbic system, including the hippocampus, amygdala, anterior cingulate, insula, and raphe nuclei (Savic et al., 2004). Merlet et al. (2004) found that reduced receptor binding was greater in the areas of seizure onset as well as in the areas where the seizure propagated. Interestingly, some antiepileptic drugs, such as pregabalin, have been shown

to reduce symptoms of anxiety by the modulation of calcium ion channels and the potentiation of GABAergic inhibition (Mula, Pini, & Cassano, 2007).

Bidirectional relationship. Many researchers have suggested that there is a complex and bidirectional relationship between anxiety and epilepsy (Adelöw et al., 2012; Kanner, 2009). In a review of seizure incidence in psychopharmacological clinical trials, researchers found high rates of seizures in the control condition, suggesting that seizure risk may be related to psychopathology (Alper, Schwartz, Kolts, & Khan, 2007). Additionally, in a review of hospitalization records, Adelöw and colleagues (2012) found a 2.7 odds ratio for an unprovoked seizure in individuals discharged with a diagnosis of anxiety. Jones and colleagues (2007) found that 45% of children with epilepsy had a psychiatric diagnosis before their first seizure and suggested that antecedent neurobiological factors may cause both anxiety and epilepsy. A bidirectional relationship between epilepsy and anxiety is supported in research completed with rats with epilepsy that exhibited anxious behaviors prior to the onset of seizures (N. C. Jones et al., 2008). Cramer, Brandenburg, and Xu (2005) suggest that higher rates of anxiety and depression in individuals with temporal-lobe epilepsy are due to common limbic pathways and neurotransmitters. Research suggests that while a causal relationship may exist between anxiety and seizures, there may also be a common underlying biological vulnerability for anxiety and seizures in individuals with epilepsy.

Seizure variables. Seizure related variables, such as duration of epilepsy, number of AEDs, seizure frequency, seizure control, seizure type, and age of seizure onset have

been consistently examined to determine their relationship to child psychopathology and anxiety. Results from this research is inconclusive, with some studies indicating that seizure and epilepsy related variables contribute to anxiety, while others find other environmental factors to be more predictive of anxiety.

Epilepsy or seizure severity. Several researchers utilized an epilepsy severity composite to approximate the impact of multiple seizure related variables. In a study of 501 children with epilepsy, researchers found that neurodevelopmental and psychiatric disorders were more prevalent in individuals with complicated epilepsy (Berg et al., 2011). However, in a study of 91 children with epilepsy Rodenburg et al. (2006) found that epilepsy factors did not significantly predict internalizing problems. Jones and colleagues (2015) echo these findings and determined that seizure severity did not differ significantly in children with or without anxiety in youth with recent onset epilepsy. The variability in the results regarding epilepsy severity are likely due to differences in how severity is defined.

Duration of epilepsy and age of onset. Findings are also mixed when duration of epilepsy is considered. In a comparison of 35 children with epilepsy and 35 healthy controls, Oguz and colleagues (2002) found that epilepsy duration was related to higher anxiety. Caplan et al. (2008) found that in 69 children with childhood absence epilepsy (CAE), children had a 1.35 greater chance of having a psychiatric diagnosis for each year of their CAE diagnosis. However, in several other studies, duration of epilepsy was not related to anxiety or general mental health (Buelow et al., 2003; Caplan et al., 2004; J. E.

Jones et al., 2015; Rodenburg et al., 2006; Schraegle & Titus, 2017a). Age of onset consistently did not predict anxiety symptoms or general mental health in children with epilepsy (Buelow et al., 2003; Caplan et al., 2004; Jones et al., 2015; Oguz et al., 2002). Discrepancies may exist in the findings due to inadequate sample sizes, differing methods of assessment, and the epilepsy types included in analyses. Additionally, duration of epilepsy may be confounded by other variables, such as the child's chronological age and age of onset (Austin & Caplan, 2007).

Seizure control. Research is inconclusive regarding the relationship between seizure control and anxiety. Researchers in Jordan found that psychiatric symptoms were higher in adolescents with medically uncontrolled epilepsy (Alwash et al., 2000). Berg and colleagues (2011) determined that after adjusting for externalizing behaviors and age, having a 5-year remission status was associated with 43% lower prevalence of internalizing symptoms. Schraegle and Titus (2017a) found that rates of anxiety were significantly higher in youth with intractable epilepsy. However, Caplan and colleagues (2004) found that prolonged seizures were not related to anxiety and Ott and colleagues (2001) also found that seizure control was not related to psychopathology. The differences in findings in the literature are likely attributed to the variety of definitions applied to seizure control and the lack of a standardized and consistent terminology for this construct.

Seizure frequency. Seizure frequency has been consistently related to symptoms of anxiety in the literature. In a study of 201 adults with epilepsy, high seizure frequency was a risk factor for anxiety (Kimiskidis et al., 2007). In a study of 35 children with epilepsy

compared to healthy controls, Oguz et al. (2002) also found that daily seizures were related to increased ratings of anxiety. Caplan and colleagues (2007) echo these findings in that youth with absence epilepsy with higher seizure frequency were significantly more likely to have a psychiatric diagnosis. In a review of differential diagnoses of psychiatric disorders in children with epilepsy, Dunn and Austin (2004) emphasized the importance of seizure frequency. While most evidence suggests that seizure frequency is related to psychopathology in youth with epilepsy, small sample sizes and relatively few studies examining anxiety in youth make it difficult to fully understand the role of seizure frequency in anxiety symptoms.

Medication. There are a variety of anti-epileptic medications that can be used to treat epilepsy and most studies are not powered to review differences between medications. Therefore, most research examining anxiety and AEDs has focused on a comparison of monotherapy and polytherapy. Caplan and colleagues (2004) did not find a relationship between AED type and anxiety. Additionally, Jones and colleagues (2015) determined that the number of AEDs did not differ significantly in children with or without anxiety. Alternatively, in a study of 101 children with epilepsy, researchers found that the number of AEDs taken was a predictor of anxiety (Williams et al., 2003). Oguz (2002) also found that polytherapy was related to higher symptoms of anxiety. Polytherapy was also a risk factor for anxiety in adolescents and adults in Nigeria (Adewuya & Ola, 2005; Fatoye, Mosaku, Komolafe, & Adewuya, 2006). Interestingly, Schraegle and Titus (2017a) found that number of AEDs did not predict anxiety in youth who had parents with a positive

history of psychopathology, but polytherapy did significantly predict anxiety in youth with parents who had no history of psychopathology. In a recent review, Reilly and colleagues (2013) suggested that increased use of AEDs leads to an increased risk for anxiety in children. However, in a recent meta-analysis of adults with epilepsy, Scott and colleagues (2017) found that rates of anxiety were not higher in individuals with epilepsy who were treated with polytherapy. It is unclear whether the effects of polytherapy would be similar for youth and adults due to the confounds of age and length of AED treatment. Additionally, it is difficult to distinguish whether higher rates of anxiety in individuals taking polytherapy are due to side effects of multiple medications or because polytherapy is an indication of more complex and difficult to control seizures, or a combination of these factors (Austin & Caplan, 2007).

Seizure type and focus. Understanding differences in rates of anxiety based on seizure type and focus would provide important information regarding the neurobiology of anxiety; however, to date, the research is limited. In a study comparing children with complex partial seizures and children with childhood absence epilepsy, Caplan and colleague (2005) found that there was a higher rate of anxiety in children with absence epilepsy. In a study of 48 children with complex partial seizures, 39 children with primary generalized epilepsy with absence seizures, and 59 healthy controls, researchers found that children with epilepsy had higher rates of psychopathology compared to healthy controls, but rates of psychopathology did not differ between the two groups with epilepsy (Ott et al., 2001). In a sample of 40 children with epilepsy who were examined prior to epilepsy

surgery, researchers found that there was no difference in rates of anxiety in children with temporal lobe epilepsy compared to children with other epilepsy types (Salpekar et al., 2013). Oguz et al., (2002) also did not find a relationship between epilepsy type and anxiety. In a study of 501 children with epilepsy, researchers found that specific subtypes of epilepsy were not related to specific psychiatric symptoms, which suggests that epilepsy has a more broad and general impact on psychopathology (Berg et al., 2011). Overall, while the number and quality of studies examining pediatric anxiety in epilepsy are limited, tentative findings suggest that rates of anxiety do not differ based on seizure type nor focus in children with epilepsy, but more research is needed.

Summary of seizure related variables. Austin and Caplan (2007) suggest that it is difficult to understand the effects of seizure related variables due to the fact that they are inter-related. Polytherapy, early age of onset, and poor seizure control are frequently inter-related and can be confounding (e.g., an individual with poor seizure control may be placed on multiple anti-epileptic medications and younger age of onset is associated with uncontrollable seizures) (Austin & Caplan, 2007). Additionally, Austin and Caplan (2007) note that a child's chronological age might also be confounded by duration of illness and age of onset (e.g., a younger child would have an early age of onset and likely shorter duration).

In a recent review of anxiety in youth with epilepsy, Reilly, Kent, and Neville (2013) concluded that some seizure variables, such as taking more than one AED, high seizure frequency, and poor seizure control were consistently associated with higher scores

on measures of anxiety. Other seizure variables, such as seizure type, age of seizure onset, and duration of epilepsy were not related to anxiety, but these findings were inconsistent across studies (Reilly et al., 2013). In a review of psychiatric disorders in children and adolescents with epilepsy, Dunn and Austin (2004) suggested that seizure syndrome, seizure severity, seizure frequency, AEDs, and family variables such as family mastery and control might be important variables to consider. They also indicated that seizure type was inconsistently predictive of psychiatric disorders (Dunn & Austin, 2004). It is clear that some seizure related variables may affect psychopathology and anxiety in children with epilepsy. However, sample sizes have been small and there are relatively few studies that examine anxiety in youth with epilepsy. More research is needed to determine whether seizure related variables have a direct effect on psychopathology or if they moderate or mediate other psychosocial variables.

Demographic variables. Age, gender, and ethnicity are consistently examined to determine whether there are differences in levels of anxiety based on these demographic variables. Oguz and colleagues (2002) found that younger children (ages 9-11) had higher ratings of trait anxiety while adolescents (ages 12-18) had higher levels of both state and trait anxiety. In a population-based study of 69 children with active epilepsy, researchers found that anxiety symptoms were higher for older children (Reilly, Atkinson, Chin, et al., 2015). In a study of 180 youth with epilepsy, older age and female gender both significantly predicted anxiety (Schraegle & Titus, 2017a). Schraegle and Titus (2017b) found that several demographic variables were related to higher anxiety symptoms, including age

(older), sex (females), and race/ethnicity (minorities). Williams et al. (2003) also found that ethnicity was a predictor of anxiety in children with epilepsy. In a study of 69 children with absence epilepsy and 103 controls, Caplan and colleagues (2008) found that girls were 5.8 times more likely to have anxiety than boys. Age and gender appear to be important demographic variables to consider when examining anxiety in youth with epilepsy.

Cognitive ability. Cognitive ability is also an important variable to consider when examining anxiety in youth with epilepsy. In a study comparing 171 kids with epilepsy, Caplan et al. (2015) found that children with epilepsy who had co-occurring affective and anxiety disorders had significantly lower IQs compared to children with epilepsy and no disorder. In a study of 164 youth with epilepsy, researchers found that there were more mental health problems in the group of children with low IQ (Buelow et al., 2003). Researchers have also found that comorbid learning problems are related to anxiety in youth with epilepsy (Williams et al., 2003). Cognitive factors are likely confounded by seizure related variables; for example, youth with epilepsy and a high IQ are more likely to have a shorter duration of illness and less severe seizures (Buelow et al., 2003).

Stigma. Individuals with epilepsy experience high levels of stigma, however, research examining the relationship between stigma and anxiety in youth with epilepsy is severely limited. Davies and colleagues (2003) suggest that there are higher rates of psychiatric diagnoses in children with epilepsy compared to other chronic illnesses because of the social stigma of epilepsy. Youth with epilepsy are also at risk for peer rejection, which can lead to experiences of social anxiety (Pinquart & Shen, 2011). Child perceptions

of stigma are related to greater child fear and worry about seizures (Austin et al., 2014). Additionally, parent and adolescent perceptions of stigma were both significant predictors of anxiety symptoms in a sample of 102 adolescents in Nigeria (Adewuya & Ola, 2005). Evidence of the role of stigma in anxiety is sparse, but preliminary evidence suggests a relationship between anxiety and perceptions of stigma.

Family variables. Family factors, such as parent-child relationships, family adaptation, parental psychopathology, and family stressors, play an important role in the development of anxiety in children with epilepsy. Only one study to date has examined the association between parent-child relationships and psychopathology in youth with epilepsy. Positive parent-child relationships were related to lower parent reported symptoms of internalizing and externalizing problems in children with epilepsy, while parental rejection led to increased ratings of internalizing and externalizing problems (Rodenburg et al., 2006). Rodenburg and colleagues (2006) also found that parental rejection mediated the relationship between problems with family adaptation and symptoms of anxiety and depression, meaning that poorer family adaptation leads to parent rejection which ultimately leads to more symptoms of anxiety/depression (Rodenburg et al., 2006). In general, family stressors are associated with higher rates of anxiety in youth with epilepsy (Adewuya & Ola, 2005; Schraegle & Titus, 2017a).

Parent history of psychopathology is another important predictor of child anxiety due to its genetic and environmental influences. In a recent review, Jones and Reilly (2016) found that parents of children with epilepsy and anxiety commonly have symptoms of

anxiety. In a study of 88 children with recent-onset of epilepsy and 49 health controls, 71% of children with epilepsy who were diagnosed with anxiety had a family member with a history of anxiety or depression, which was significantly different when compared to children with epilepsy without anxiety (37%) and control subjects (25%) (Jones et al., 2015). Adewuya and Ola (2005) also found that youth anxiety was related to parental psychopathology. In a recent analysis of 180 children with epilepsy, Schraegle and Titus (2017a) found that parental psychiatric history was related to a 3-fold risk for anxiety; this increased to a 4-fold risk for anxiety in the context of intractable epilepsy. Schraegle and Titus (2017a) also found that the factors that contribute to anxiety differ in the context of parental anxiety (e.g., AEDs were related to anxiety in those children with a parent with no psychiatric history, but AEDs were unrelated to anxiety in children with a parent with psychiatric history). Parent anxiety is common in children with epilepsy and it is associated in lower quality of life (C. Jones & Reilly, 2016; Schraegle & Titus, 2017b). Despite the importance of family factors on child anxiety in the literature, research in youth with epilepsy is limited.

Anxiety and health related quality of life in epilepsy. Health related quality of life (HRQoL) is an individual's perceptions of quality of life relative to their health or disease status (Bakas et al., 2012). In a prospective, community-based study, psychiatric comorbidity in child-onset epilepsy was more highly correlated with HRQoL than remission status (Baca, Vickrey, Caplan, Vassar, & Berg, 2011). Additionally, Baca and colleagues (2011) found that internalizing psychiatric comorbidity was associated with

worse HRQoL, while externalizing symptoms had no relationship to HRQoL. In a study of 60 children with epilepsy in Serbia, researchers found that depression, generalized anxiety symptoms, and separation anxiety symptoms had the most significant impact on quality of life compared to other demographic and epilepsy variables (Stevanovic et al., 2011). When examining domains of quality of life, lower internalizing symptoms were related to better physical and emotional quality of life (Loiselle et al., 2016). In a study of HRQoL in 109 children with pediatric epilepsy after surgery, researchers found that improved seizure freedom in the last twelve months was associated with better HRQoL and that symptoms of anxiety and depression mediated this relationship; in other words, seizure freedom led to better parent ratings of anxiety and depression which led to better HRQoL (Puka & Smith, 2015). Symptoms of anxiety in youth with epilepsy have significant effects on quality of life.

Statement of the Problem and Purpose

There are a multitude of factors that put youth with epilepsy at an increased risk of anxiety, including biological, psychosocial, demographic, and family factors; these factors likely interact and influence each other. Despite the clear relationship between anxiety and epilepsy, anxiety has been considered the "forgotten" disorder in epilepsy research and has been overshadowed by research in depression (Clary, 2014). In the research that has been conducted about anxiety in youth with epilepsy, there has been no underlying theoretical background for the selection of variables and researchers have used inappropriate measures (Gandy, Sharpe, & Perry, 2012). Additionally, in clinical care anxiety is severely

underdiagnosed and only a third of diagnosed children actually receive mental health services (Caplan et al., 2005). Furthermore, a recent ILAE Task Force Report suggested that it is important to assess for reversible causes of anxiety (Dunn et al., 2016). Examining family factors and psychosocial difficulties associated with anxiety in youth with epilepsy is especially important because it may help to identify accessible and modifiable targets for intervention. There is a clear need for more research investigating the risk and protective factors for anxiety in youth with epilepsy. This proposed research study will examine how seizure severity and parent factors (i.e., history of psychopathology, illness cognitions, and perceptions of stigma) interact to influence anxiety in youth with epilepsy.

Research Questions and Hypotheses

Research question 1. To what extent do parent factors influence anxiety in youth with epilepsy?

Hypothesis 1a. Youth with epilepsy who have a parent with a history of psychopathology will have more parent reported anxiety features.

Rationale 1a. Parent psychopathology is an important predictor of child anxiety due genetic and environmental factors. Heritability estimates are in the range of 30-40% for anxiety (Hettema et al., 2001; Micco et al., 2009). Parent history of psychopathology may also lead to environmental factors (e.g., socialization, modeling, and accommodation) that make children more vulnerable to anxiety (Murray et al., 2009). In the general population, children of parents with anxiety are four times more likely to have anxiety than children without a parent with anxiety (Micco et al., 2009) and youth with epilepsy who

have parents with a history of psychopathology are also at increased risk for anxiety (Adewuya & Ola, 2005; Jones et al., 2015; Schraegle & Titus, 2017a).

Hypothesis 1b. Elevated parent perceptions of stigma will be related to increased parent reported anxiety features in youth with epilepsy.

Rationale 1b. Many researchers have hypothesized that higher rates of anxiety in youth with epilepsy are related to the social stigma of epilepsy (Davies et al., 2003; Hermann et al., 1988). However, relatively few studies have systematically examined this issue. Some researchers have found that higher perceptions of stigma are related to more worry (Austin, MacLeod, Dunn, Shen, & Perkins, 2004; Austin et al., 2014) and one research group found that anxiety was predicted by both parent and adolescent perceptions of stigma (Adewuya & Ola, 2005). Parents with higher perceived stigma may also engage in more overprotective parenting behaviors that increase the risk for anxiety in children (Anthony, Gil, & Schanberg, 2003).

Hypothesis 1c: Negative parent illness cognitions will be related to increased parent reported anxiety features in youth with epilepsy.

Rationale 1c. Parent illness cognitions, particularly cognitions of helplessness, may lead to higher rates of anxiety in children through several pathways, including increased parent distress, modeling of anxious cognitions and behaviors, and parenting behaviors. Negative parent illness cognitions and difficulty coping with a child's illness are related to parent distress, which is associated with emotional distress in the child (Colletti et al., 2008; Nicolaas et al., 2016; Robinson, Gerhardt, Vannatta, & Noll, 2007; Steele, Dreyer, &

Phipps, 2004). Parents with cognitions of helplessness may model anxious behavior and influence illness cognitions in their child (Burstein & Ginsburg, 2010) and individuals with poor illness cognitions have poorer emotional health (Hudson, Bundy, Coventry, & Dickens, 2014). A parent's feelings of helplessness might also influence the child's perceptions of control over their environment (Chorpita & Barlow, 1998). Parents may also engage in parenting behaviors, such as overprotection, which can make a child more vulnerable to anxiety by limiting the child's engagement in the environment (Anthony et al., 2003).

In contrast to parent cognitions of helplessness, parent cognitions of acceptance may be related to less distress, positive modeling, and parenting behaviors that are protective factors for child anxiety. Parents who engage in acceptance cognitions may be less distressed, which is associated with better emotional adjustment in children (Nicolaas et al., 2016). Additionally, parents with cognitions of acceptance may model more adaptive coping behavior and cognitions and engage in parenting behavior that allows the child to engage in behaviors that increase their perceptions of control over their environment (Burstein & Ginsburg, 2010; Chorpita & Barlow, 1998).

Research question 2. To what extent do parent factors mediate the effect of parent history of psychopathology on anxiety in youth with epilepsy?

Hypothesis 2a: Parent perceptions of stigma will partially mediate the effect of parent history of psychopathology on parent reported anxiety features in youth with epilepsy.

Rationale 2a. Parents with a history of psychopathology will have more perceptions of stigma, which will impact their ratings of child anxiety. Parents with more negative mood are more likely to report greater perceptions of stigma (Austin et al., 2004). Parent history of psychopathology will lead to negative perceptions of stigma, which will ultimately lead to higher ratings of anxiety in youth with epilepsy.

Hypothesis 2b: Negative parent illness cognitions will partially mediate the effect of parent history of psychopathology on parent reported anxiety features in youth with epilepsy.

Rationale 2b. Parents with a history of psychopathology will have more negative illness cognitions, which will impact their ratings of child anxiety. Parents who are clinically distressed have more cognitions of helplessness and fewer cognitions of acceptance (Nicolaas et al., 2016). Additionally, parent cognitions of helplessness are correlated with worse psychological well-being, while parent cognitions of acceptance are associated with better psychological well-being (Nicolaas et al., 2016). Parent history of psychopathology will lead to negative illness cognitions, which will ultimately lead to higher ratings of anxiety features in youth with epilepsy.

Research question 3. To what extent does seizure severity influence the impact of parent factors on anxiety in youth with epilepsy?

Hypothesis 3a. Seizure severity will moderate the effect of parent history of psychopathology on parent perceived stigma.

Rationale 3a. This hypothesis is supported by Austin et al. (2004), who found that greater parent perceptions of stigma are associated with greater seizure severity. Additionally, Schraegle and Titus (2017a) found differential effects of AEDs for parents with and without a history of psychopathology. AEDs were related to anxiety in youth without a parent with a history of psychopathology, but AEDS were not related to anxiety in youth with a parent with a history of psychopathology (Schraegle & Titus, 2017a). There may be a similar interaction between parent history of psychopathology and seizure severity on parent perceptions of stigma. Parents with a history of psychopathology might have higher perceptions of stigma regardless of their child's seizure severity, while parents with no history of psychopathology may only be at risk of higher perceptions of stigma in the context of greater seizure severity. See Figure 3.

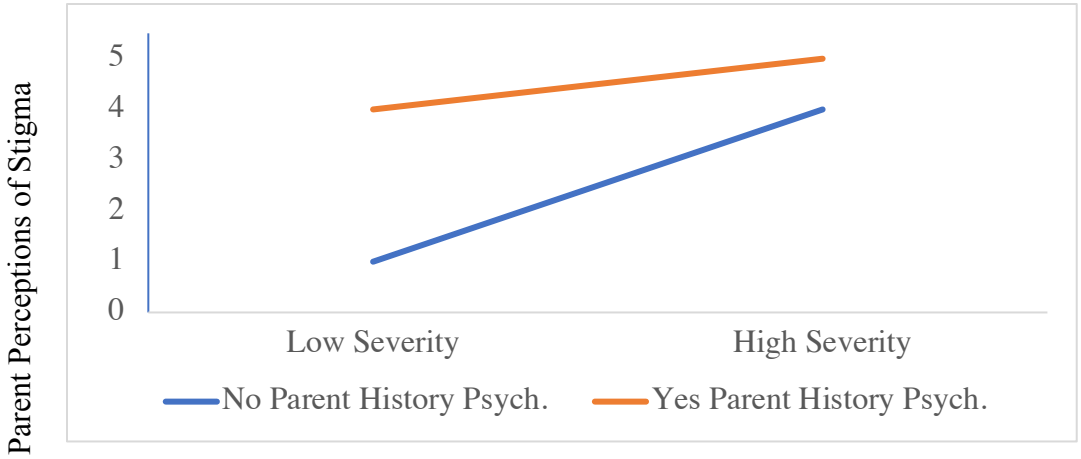

Figure 3: *Hypothesized moderation on parent perceptions of stigma*. This figure illustrates the hypothesized interaction between parent history of psychopathology and seizure severity on parent perceptions of stigma. The red line represents the hypothetical regression of seizure severity on parent perceptions of stigma in parents with a history of psychopathology, while the blue line represents the hypothetical regression of seizure severity on parent perceptions of stigma in parents without a history of psychopathology. A higher score indicates more negative perceptions of stigma.

Hypothesis 3b. Seizure severity will moderate the effect of parent history of psychopathology on parent illness cognitions.

Rationale 3b. AEDs are a predictor of anxiety in youth with a parent with no history of psychopathology, while AEDs are not a predictor of anxiety in youth with a parent with a history of psychopathology (Schraegle & Titus, 2017a). Seizure severity may have a similar interaction with parent history of psychopathology on parent illness cognitions. Parents without a history of psychopathology may be more vulnerable to negative illness cognitions in the context of greater seizure severity, while parents with a history of psychopathology may be more susceptible to negative coping cognitions regardless of the context. See Figure 4.

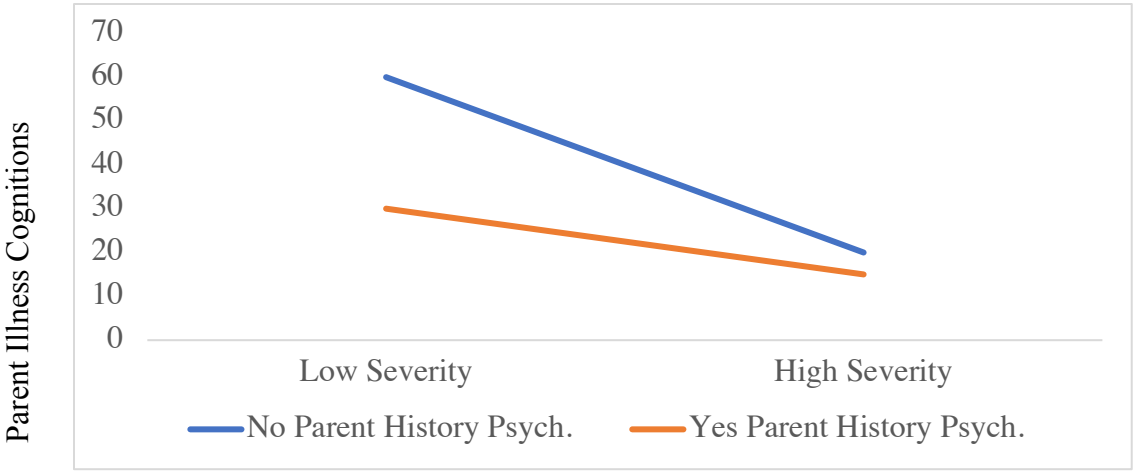

Figure 4: *Hypothesized moderation on parent illness cognitions*. This figure illustrates the hypothesized interaction between parent history of psychopathology and seizure severity on parent illness cognitions. The red line represents the hypothetical regression of seizure severity on parent illness cognitions in parents with a history of psychopathology, while the blue line represents the hypothetical regression of seizure severity on parent illness cognitions in parents with a history of psychopathology. A lower score indicates more negative illness cognitions.

Research question 4. To what extent do family factors, anxiety, and seizure severity influence quality of life in youth with epilepsy?

Hypothesis 4. Increased seizure severity, features of anxiety, parent perceptions of stigma, and negative parent illness cognitions will be related to decreased health related quality of life in youth with epilepsy.

Rationale 4. Many seizure variables, including polytherapy and increased seizure frequency, have been associated with decreased quality of life in youth with epilepsy (Baca et al., 2011; Conway et al., 2016; Puka & Smith, 2015). Internalizing symptoms, such as anxiety and depression, have frequently been associated with decreased quality of life in

individuals with epilepsy (Baca et al., 2011; Conway et al., 2016; Loiselle et al., 2016; Puka & Smith, 2015; Reilly, Atkinson, Das, et al., 2015b; Stevanovic et al., 2011). Moreover, some researchers suggest that internalizing symptoms have the most significant effect on quality of life (Stevanovic et al., 2011) and that anxiety and depression mediate the relationship between seizure control and quality of life (Puka & Smith, 2015). Research into the effect of family factors is more limited, but some research suggests that parent anxiety is associated with decreased quality of life (Jones & Reilly, 2016; Schraegle & Titus, 2017a).

Hypothesized model. Taken together, these hypotheses suggest that anxiety may influenced by parent factors in several ways. First, parent history of psychopathology is hypothesized to have a direct influence on anxiety through genetic and environmental factors. Parent illness cognitions and parent perceptions of stigma are also hypothesized to influence anxiety, and these parent factors are hypothesized to partially mediate the relation between parent history of psychopathology and anxiety. Finally, seizure severity is hypothesized to moderate the impact of parent history of psychopathology on parent perceived stigma and parent illness cognitions. See Figures 5 and 6.

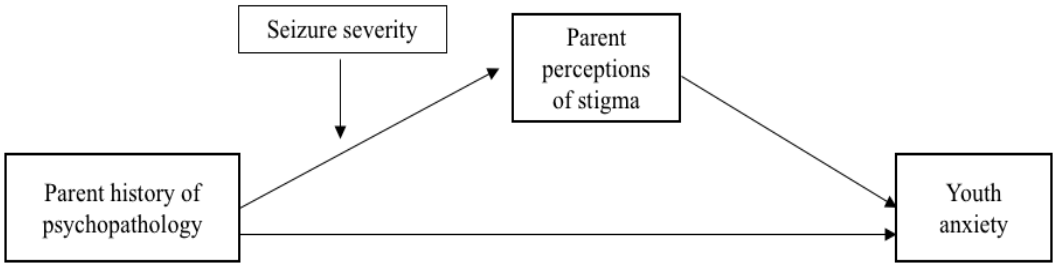

Figure 5: *Hypothesized model including parent perceptions of stigma*. This figure illustrates the hypothesized relations between parent history of psychopathology, parent perceptions of stigma, seizure severity, and anxiety in pediatric epilepsy.

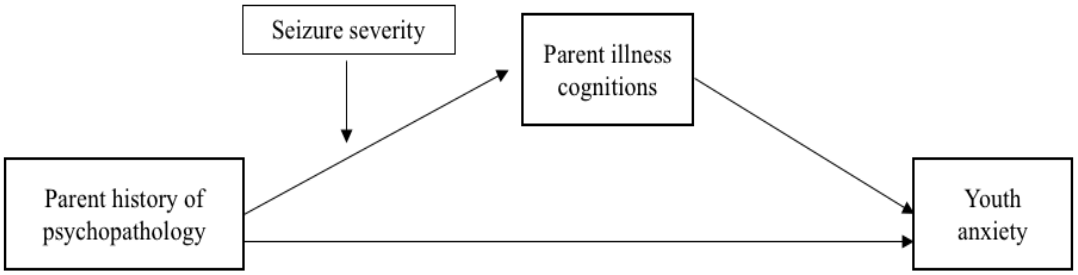

Figure 6: *Hypothesized model including parent illness cognitions*. This figure illustrates the hypothesized relations between parent history of psychopathology, parent perceptions illness cognitions, seizure severity, and anxiety in pediatric epilepsy.

It is important to note that this is a cross-sectional study and the data used in this research are nonexperimental in nature; there was no experimental manipulation of seizure severity, parent perceptions of stigma, parent illness cognitions, or parent history of

psychopathology to determine their subsequent effect on parent reported anxiety. Therefore, all statements that discuss the "effect" or "influence" of one variable on another are dependent on the validity of this model. "If the model is a reasonable representation of reality, the estimates resulting from the model indeed show the extent of the influence of one variable on another. If the model is not a reasonable representation of reality, the estimates are not accurate estimates of those effects." (Disclaimer adapted from Keith [2014]).

Chapter 3: Methods

Participants

Participants in this study included 121 children and adolescents with epilepsy who were referred to a tertiary outpatient clinic in Central Texas by their neurologists for a neuropsychological evaluation to assist with treatment planning. Youth were considered for inclusion in the study if they were between the ages of 6-18 and were diagnosed with epilepsy by a neurologist. Youth were excluded from the study if the caregiver or child did not speak English or if the parent or caregiver did not consent for their child's information to be used for research purposes.

Procedures

Parents of youth with epilepsy who were referred for neuropsychological evaluation were consented during the assessment intake. The primary caregiver was asked to complete an intake questionnaire and measures related to their child's health and epilepsy. All parents also completed a clinical intake interview regarding their child's medical, psychosocial, and family history with a licensed psychologist. Medical records were reviewed for all patients whose parents provided written and oral consent for their results to be used for research purposes. Institutional review board approval was obtained for all data collection procedures.

Measures

Demographic information. Demographic information was obtained via review of medical records, intake questionnaires, and parent interviews. Variables included: gender, race/ethnicity, child's age, and maternal education (coded as 1= less than high school, 2=high school degree, 3= some college, 4=college degree, 5=graduate degree).

Seizure information. Seizure-related variables were extracted from medical records, intake questionnaires, and parent interviews. Variables included: age at seizure onset, duration of epilepsy, number of AEDs (coded as 0=no AED treatment, 1=monotherapy, 2=polytherapy), seizure frequency (coded as 0=none in past year, 1=yearly, 2=quarterly or monthly, 3=weekly or daily), epilepsy type (coded as 0=no seizures in the past year, 1=absence seizures, 2=focal seizures, 3=generalized tonic-clonic, 4=multiple seizure types), and intractability status (coded as 0=not intractable and 1=intractable, using the ILAE task force definition of drug-resistant epilepsy) (Kwan et al., 2010). Seizure severity was a composite variable, similar to the approach of Rodenberg et al. (2006) and Austin et al. (1996), calculated as a sum of the values for epilepsy type, number of AEDs, and seizure frequency.

Parent history of psychopathology. Information regarding parent history of psychopathology was obtained from family history reported by parents on the intake questionnaires and parent interviews. Parent psychiatric history was reviewed for presence of anxiety, depression, and/or bipolar disorder and was coded as 1 (present) or 0 (absent).

Anxiety. Anxiety was measured using Parent Rating Scales (PRS) from the Behavior Assessment System for Children (BASC) second and third editions (Kamphaus & Reynolds, 2015; Reynolds & Kamphaus, 2004). A majority of parents completed the BASC-3 (n=76; 62.8%). The BASC-3 contains all of the same items found on the BASC-2 and includes some additional items. The BASC-2 and BASC-3 anxiety scales are very highly correlated (r=0.97-0.98) (Kamphaus & Reynolds, 2015). The BASC PRS Child Form (ages 6:0-11:11) and the PRS Adolescent Form (ages 12:0-21:11) were used depending on the age of the child during the assessment. The BASC PRS anxiety scale has 11 to 14 items that the parent rated according to the frequency of their child's behavior (never, sometimes, often, or almost always). Raw scores were converted to T-scores, with T-scores of 60-69 considered in the "at risk" range and T-scores ≥70 considered in the "clinically significant" range.

The BASC-2 was normed using 1,800 parents for each form version and the sample was designed to represent the US population (from the 2001 Current Population Survey) with respect to gender, race/ethnicity, socioeconomic status, geographic region, and special education classification. The anxiety scale has good internal-consistency reliability (coefficient alpha ranging from 0.81-0.85) and test-retest reliability (corrected r=0.73-0.86). Inter-rater reliability is moderate (corrected r=0.66-0.80) (Reynolds & Kamphaus, 2004). The standard error of measurement ranges from 3.9 to 4.44 (Reynolds & Kamphaus, 2004).

The BASC-3 was normed using 600 parents for each form version and the sample was designed to represent the US population with respect to gender, race/ethnicity, socioeconomic status, geographic region, and special education classification. The anxiety scale has good internal-consistency reliability (coefficient alpha ranging from 0.83-0.89) and test-retest reliability (corrected r=0.85-0.90). Inter-rater reliability is moderate (corrected r=0.54-0.65) (Kamphaus & Reynolds, 2015). The standard error of measurement ranges from 3.32 to 4.12 (Kamphaus & Reynolds, 2015).

In terms of validity, the BASC has good internal structure. There are low to moderate correlations between the BASC-3 anxiety scale and the AESEBA Anxiety/Depression scale (r= 0.46-0.63) and between the BASC-2 anxiety scale and the AESEBA Anxiety/Depression scale (r= 0.48-0.71). The BASC PRS has been widely used in research with pediatric epilepsy populations (Bender et al., 2008; Titus, Kanive, Sanders, & Blackburn, 2008; Vega et al., 2011).

Stigma. Parent perceptions of stigma were assessed using the Epilepsy Stigma Scale (Austin et al., 2004). Stigma was defined by the authors of the measure as "referring to an attribute (i.e., seizure condition) held by a person that leads to his or her being discredited or devalued by others" (Austin et al., 2004). The parent version of the form measures parent perceptions of how epilepsy affects others' perceptions of their child (Austin et al., 2004). The parent version of the Epilepsy Stigma Scale consists of five items rated on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), with questions like "people who know my child has a seizure condition treat him/her

differently." The items were summed and divided by the number of items to provide a stigma score; a higher score reflected greater perceptions of stigma related to epilepsy (Austin et al., 2004).

The psychometric properties of the scale were assessed with 171 parents of children (ages 9-14) with chronic epilepsy and 224 parents of children (ages 4-14) with new-onset epilepsy. Factor analysis of the stigma scale revealed that one factor accounted for 100% of the variance, factor loadings for each question ranged from 0.63 to 0.84, and found flat scree plots after the first factor; this suggests that the scale measures one unitary construct (Austin et al., 2004). The Epilepsy Stigma Scale also demonstrates good internal consistency (coefficient alpha ranging from 0.77-0.79) (Austin et al., 2004). In this sample, the Epilepsy Stigma Scale demonstrated good internal consistency (Chronbach's alpha 0.79). Overall, the Epilepsy Stigma Scale has good psychometric properties and appears to measure one construct.

Illness cognitions. Parent illness cognitions were measured using the Illness Cognition Questionnaire-Parent Version (ICQ-P) (Nicolaas et al., 2016). The ICQ-P was adapted from the Illness Cognition Questionnaire (ICQ), which was originally developed for adults with chronic health conditions (Evers et al., 2001). The ICQ-P measures a parent's cognitions about how they evaluate their child's illness. The ICQ-P consists of three subscales: helplessness (e.g., my child's illness prevents me from doing what I would really like to do), acceptance (e.g., I can cope effectively with my child's illness), and disease benefits (e.g., my child's illness has helped me realize what is important in life)

(Nicolaas et al., 2016). The ICQ-P consists of 18 items rated on a 4-point Likert scale (1= not at all, 2=somewhat, 3=to a large extent, 4=completely). The scores are calculated by summing the items scores; subscale scores range from 6 to 24 and the total score ranges from 18 to 72.

The psychometric properties of the scale were originally assessed with 242 parents of children aged 0 to 17 with cancer (Nicolaas et al., 2016). Factor analysis revealed that three factors accounted for 59.1% of the variance. Each subscale has adequate internal consistency (Chronbach's alpha 0.80-0.88) (Nicolaas et al., 2016). In this sample, it also demonstrated adequate internal consistency for the total score (Chronbach's alpha 0.71) and for each subscale (Chronbach's alpha 0.71-0.86). Parent cognitions of helplessness were moderately correlated with worse psychological well-being and parents who were clinically distressed had more cognitions of helplessness (Nicolaas et al., 2016). Parent cognitions of acceptance were moderately to highly associated with better psychological well-being and parents who were clinically distressed had fewer cognitions of acceptance (Nicolaas et al., 2016). The ICQ-P has been used within the epilepsy population (McLaughlin, Schraegle, Nussbaum, & Titus, 2016; McLaughlin, Schraegle, & Titus, 2017).

Quality of life. Health related quality of life (HRQOL) was measured using the Quality of Life in Childhood Epilepsy (QOLCE) and the Quality of Life in Childhood Epilepsy-55 (QOLCE-55), which are both parent reported measures of quality of life designed specifically for children and adolescents with epilepsy ages 4-18.

The QOLCE consists of 91 items rated on a five-point Likert scale ranging from "very often" or "all of the time" to "never" or "none of the time;" other questions range from "yes, limited a lot" to "no, not limited" and "excellent" to "poor," depending on item content. The QOLCE measures HRQOL across a variety of functional life domains, including: physical functioning, emotional well-being, cognitive functioning, social functioning, and behavior (Sabaz et al., 2000). The QOLCE-55 was developed using a principal component analysis of the QOLCE to reduce the number of items (Goodwin, Lambrinos, Ferro, Sabaz, & Speechley, 2015). The QOLCE-55 consists of 55 items rated on a five-point Likert scale ranging from "very often" or "all of the time" to "never" or "none of the time;" other questions range from "yes, limited a lot" to "no, not limited," depending on item content. Factor analysis of the QOLCE-55 indicated a four-factor model of HRQOL, including cognitive, emotional, social, and physical domains. The overall QOLCE-55 score demonstrates high internal consistency (Cronbach's alpha =0.96), and the individual subscales have similarly robust internal consistency (Cronbach's alpha = 0.82-0.97) (Goodwin et al., 2015). Convergent validity with theoretically similar constructs is adequate (ρ = 0.38) (Goodwin et al., 2015).

Most parents completed the QOLCE-55 (n=82; 67.8%); however, for those that completed the QOLCE, items were extracted and re-scored according to the QOLCE-55 due to its stronger psychometric properties (Goodwin et al., 2015). The QOLCE-55 was scored using a linear transformation of raw scores to a 0–100-point scale, where higher

scores indicate a higher level of HRQOL. An overall quality of life score was calculated as the sum of scores from all domains.

Cognitive functioning. Intelligence was assessed using the Wechsler Adult Intelligence Scale-IV (WAIS-IV), the Wechsler Intelligence Scale for Children-IV (WISC-IV), the Wechsler Intelligence Scale for Children-V (WISC-V), or the Kaufman Assessment Battery for Children, Second Edition (KABC-II) based on the age of the child at the time of testing and clinical judgment. The Wechsler intelligence scales and the Kaufman Assessment Battery for Children are widely used measures of cognitive functioning. The KABC-II is designed for use with children between the ages of 3:0 and 18:11. WISC-IV and WISC-V are designed for use with children between the ages of 6:0 and 16:11 and the WAIS-IV is designed for use in individuals between the ages of 16:00 and 90:11.

The WISC-IV and WISC-V were both normed on samples of 2,200 children stratified on U.S. Census data (March 2000 for WISC-IV and October 2012 for WISC-V) to match population characteristics related to age, sex, race/ethnicity, geographic region, and self or parent education level. The WAIS-IV was normed on a sample of 2,200 adults stratified by U.S. Census data (October 2005) to match population characteristics related to age, sex, race/ethnicity, geographic region, and parent education level. The Full Scale IQ (FSIQ) is a measure of global cognitive ability that is derived from seven subtests from the WISC-V and WISC-IV. The FSIQ on the WAIS-IV is derived from ten subtests. The reported internal reliability coefficient for the FSIQ is 0.96, 0.96, and 0.98 for the WISC-

IV, the WISC-V, and the WAIS-IV, respectively. The corrected *r* for test-retest reliability for the FSIQ is 0.91, 0.92, and 0.96 for the WISC-IV, the WISC-V, and the WAIS-IV, respectively (Wechsler, 2003, 2008, 2014). The KABC-II was normed on a sample of 3,025 children stratified on U.S. Census data (2001) to match population characteristics related to gender, ethnicity, parent education, geographic region, and educational and psychological classification (Kaufman & Kaufman, 2004). The Fluid-Crystalized Index (FCI) is a composite measure of cognitive ability that is derived from ten subtests on the KABC-II. The reported split-half reliability coefficient for the FCI on the KABC-II ranges from .94 to .97. The adjusted *r* for test-retest reliability of the FCI on the KABC-II ranges from .90 to .94 (Kaufman & Kaufman, 2004).

Most youth were assessed using the WISC-V (n=73; 60.4%). However, due to the necessity to assess patients with epilepsy with the same instrument before and after epilepsy surgery, some patients were administered the WISC-IV (n=8; 6.4%). There are many similarities between the two versions of the WISC, but some of the subtests are not identical and they were normed on different populations. The developers report strong correlations between the FSIQ index on the WISC-IV and the WISC V (corrected *r* of 0.86) (Wechsler, 2003, 2014). Some younger children were administered the KABC-2 (n=15; 12.4%), and there are moderate correlations between the FCI index on the KABC-II and the FSIQ on the WISC-IV and the WISC V, (adjusted r=0.89 and r=0.81, respectively) (Kaufman & Kaufman, 2004; Wechsler, 2014). Older adolescents were administered the WAIS-IV (n=25; 20.7%), and there are also strong correlations on the FSIQ index between

the WAIS-IV and the WISC-IV (corrected *r* of 0.91) and between the WAIS-IV and the WISC-V (corrected *r* of 0.89) (Wechsler, 2003, 2008, 2014).

Analyses

Preliminary analyses. Preparation of the data and preliminary analyses were conducted using SPSS 22.0. Results of a power analysis indicated that to detect a small to medium effect size of $f^2 = 0.1$ with power of 0.80 at an alpha level of 0.01 a total of 121 participants were necessary (Faul, Erdfelder, Lang, & Buchner, 2007). Estimates for a sample size needed for a bias-corrected bootstrap with a medium effect size for the α path and a small to medium effect size for the β path was approximately 116 (Fritz & MacKinnon, 2007). Descriptive statistics (means, ranges, standard deviations, minimum and maximum values) were calculated for each of the criterion variables. Correlations between all variables were also assessed.

Analysis of the research questions. Analyses consisted of a series of multiple regressions and tests of mediation and moderation using the Hayes (2013) PROCESS Macro in SPSS version 22.0. To ensure that no assumptions were violated, the data were assessed for linearity, independence of errors, homoscedasticity (variance of errors), normality of residuals, approximate normality of distribution, and outliers (Keith, 2014). Statistical assumptions were examined, and no violations were detected. The data were also assessed for multicollinearity by assessing tolerance (independence of independent variables) and the variance inflation factor (Keith, 2014).

PROCESS is a free statistical tool for use on SPSS that completes mediation and moderation analyses using path-analysis. The PROCESS mediation model uses bootstrapping, which is a resampling method, to determine indirect effects. Bootstrapping generates an "empirically derived representation of the sampling distribution of the indirect effect," which is then used to generate a confidence interval for the indirect effect (Hayes, 2013). PROCESS uses a bias-corrected bootstrap confidence interval (using 10,000 bootstrap samples), which is a recommended approach for inferring indirect effects in mediation analyses (Hayes, 2013). Bootstrapping is the generally preferred method compared to Sobel tests (or the normal theory approach) in mediation analyses because it has higher power (less conservative), does not assume normality of sampling distribution, and tends to be more accurate (Hayes, 2013). The process mediation model is also preferable to the Baron and Kenny (1986) approach because it quantifies the indirect effect and uses an inferential test, it is more powerful, it does not require that the independent variable affects the dependent variable, and it allows quantification and comparison of different indirect effects (Hayes, 2013).

Selection of control variables. Control variables were selected based on demographic factors that are related to the outcome variables of interest. Age, gender, and cognitive functioning (IQ) were controlled for in research questions 1-3 due to the relationship of these demographic factors with anxiety, stigma, and illness cognitions in the general and epilepsy population (Buelow et al., 2003; Caplan et al., 2005; Caplan et al., 2008; Caplan et al., 2015; Oguz et al., 2002; Reilly, Atkinson, Chin, et. al., 2015; Schraegle

& Titus, 2017a; Williams et al., 2003). Cognitive functioning (IQ) was controlled for in research question 4 due to its known impact on quality of life in epilepsy (e.g., Conway, Widjaja, & Smith, 2018).

Research question 1. To what extent do parent factors influence anxiety in youth with epilepsy?

Analysis for research question 1. To test hypotheses 1a-1c, separate sequential multiple regression analyses were conducted. The BASC anxiety T-score was regressed on parent history of psychopathology (positive history or no history) controlling for IQ, gender, and age, on parent perceptions of stigma (average score) controlling for IQ, gender, and age, and on parent illness cognitions (total score) controlling for IQ, gender, and age.

Research question 2. To what extent do parent factors mediate the effect of parent history of psychopathology on anxiety in youth with epilepsy?

Analysis for research question 2. To test hypotheses 2a and 2b, mediations were assessed with a bias-corrected bootstrap confidence interval using the PROCESS macro (Hayes, 2013) to determine the indirect effect of parent history of psychopathology on the BASC anxiety T-score through parent perceptions of stigma (average score), controlling for IQ, gender, and age, and through parent illness cognitions (total score), controlling for IQ, gender, and age.

Research question 3. To what extent does seizure severity influence the impact of parent factors on anxiety in youth with epilepsy?

Analysis for research question 3. To test hypotheses 3a and 3b, moderation was assessed with a simple moderation model using the PROCESS macro (Hayes, 2013). The PROCESS model generated the conditional effects of parent history of psychopathology on parent perceptions of stigma at varying levels of seizure severity controlling for IQ, gender, and age and the conditional effects of parent history of psychopathology on parent illness cognitions at varying levels of seizure severity controlling for IQ, gender, and age.

Research question 4. To what extent do family factors, features of anxiety, and seizure severity influence quality of life in youth with epilepsy?

Analysis for research question 4. To test hypothesis 4, a simultaneous multiple regression analysis was conducted. Total HRQOL was regressed on seizure severity, anxiety, parent perceptions of stigma, and parent illness cognitions controlling for IQ.

Chapter 4: Results

The purpose of this study was to examine parent reported anxiety in pediatric epilepsy and the role of seizure severity, parent history of psychopathology, parent illness cognitions, and parent perceptions of stigma as well as the impact of these variables on Health-Related Quality of Life (HRQOL). All statistical analyses were performed using SPSS (version 22.0).

Preliminary Data Analysis

Descriptive statistics. Descriptive statistics regarding demographic characteristics, such as IQ, age at evaluation, gender, race/ethnicity, parent history of psychopathology, and maternal education can be found in Table 1. Youth were between the ages of 6 and 18 (*M*=12.43; *SD*=3.76). A slight majority of patients were female (57%). IQ scores ranged from 40 to 123 (*M*=78.08; *SD*=18.53). 28.9% of youth with epilepsy had a parent with a history of psychopathology.

Table 1: Demographic characteristics.

	n (%)	Mean (*SD*)
IQ	--	78.08 (18.53)
Age	--	12.43 (3.76)
Gender		
Female	69 (57)	--
Male	52 (43)	--
Race/Ethnicity		
White, Non-Hispanic	58 (47.9)	--
White, Hispanic	30 (24.8)	--
Black/African American	8 (6.6)	--
Asian/Asian American	5 (4.1)	--
Other	9 (7.4)	--
Missing/Decline to state	11 (9.1)	--
Parent history of psychopathology		
Absent	83 (68.6)	--
Present	35 (28.9)	--
Maternal Education		
< High school degree	5 (4.1)	--
High school degree	26 (21.5)	--
Some college	28 (23.1)	--
College degree	33 (27.3)	--
Graduate degree	15 (12.4)	--

Descriptive statistics regarding epilepsy characteristics can be found in Table 2. Epilepsy age of onset ranged from infancy to 16 years (*M*=5.90; *SD*=4.62). Duration of epilepsy ranged from 2 months to 18 years (*M*=6.57; *SD*=4.27). The seizure severity composite ranged from 0 to 9 (*M*=4.83, *SD*=2.43). Most youth were on polytherapy (47.9%) or monotherapy (39.7%) antiepileptic drug treatment. A majority of youth experienced focal epilepsy (49.6%) and 26 patients (21.5%) did not experience a seizure in the past year.

Table 2: Epilepsy characteristics.

	n (%)	Mean (*SD*)
Age of onset (years)	--	5.90 (4.62)
Duration (years)	--	6.57 (4.27)
Seizure severity	--	4.83 (2.43)
Antiepileptic drug type		
None	15 (12.4)	--
Monotherapy	48 (39.7)	--
Polytherapy	58 (47.9)	--
Intractability status		
Intractable	65 (53.7)	--
Not intractable	56 (46.3)	--
Epilepsy type		
No seizures in past year	26 (21.5)	--
Absence	10 (8.3)	--
Focal	60 (49.6)	--
Generalized tonic-clonic	21 (17.4)	--
Multiple seizure types	4 (3.3)	--
Seizure frequency		
None in past year	26 (21.5)	--
Yearly	12 (9.9)	--
Quarterly	49 (40.5)	--
Weekly or daily	34 (28.1)	--

Descriptive statistics regarding the different parent reported measures can be found in Table 3. On the BASC, 21 parents endorsed anxiety features in the at-risk range for their child (T-scores 60-69; 17.4%) and 10 parents endorsed anxiety features in the clinically significant range for their child (T-scores ≥70; 8.3%). T-scores on the BASC Anxiety scale ranged from 32 to 82, with mean scores in the average range (*M*=52.60*; SD*=10.77). Parent perceptions of stigma ranged from 1 to 4 (*M*=2.44; *SD*=0.88). Total illness cognitions scores ranged from 42 to 72 (*M*=62.16; *SD*=6.65). Quality of life scores ranged from 20.25 to 93.95 (*M*=62.72; *SD*=15.65).

Table 3: Parent reported questionnaires.

	n (%)	Mean (*SD*)
Anxiety	--	52.60 (10.77)
At-risk	21 (17.4)	--
Clinically significant	10 (8.3)	--
Stigma	--	2.44 (0.88)
Illness Cognitions Total	--	62.16 (6.65)
Acceptance	--	20.83 (2.95)
Helplessness	--	8.95 (2.77)
Perceived benefits	--	20.28 (3.85)
Quality of Life Total	--	62.72 (15.65)
Cognitive	--	49.67 (20.16)
Emotional	--	72.83 (12.90)
Social	--	74.98 (24.73)
Physical	--	53.30 (22.22)

Table 4 represents the correlation matrix of the outcome variables and all independent variables of interest.

Table 4: Correlation matrix.

	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. Anxiety	1	--	--	--	--	--	--	--	--
2. IQ	.139	1	--	--	--	--	--	--	--
3. Age	.032	.086	1	--	--	--	--	--	--
4. Gender	.128	.033	.056	1	--	--	--	--	--
5. Maternal education	-.015	-.192*	-.026	-.007	1	--	--	--	--
6. Parent history	.204*	.102	.019	-.006	-.038	1	--	--	--
7. Stigma	.190*	-.237**	.089	-.066	.038	.101	1	--	--
8. Illness cognitions	-.131	-.041	-.127	-.078	-.249**	-.081	-.251**	1	--
9. Seizure severity	.019	-.297**	.100	.134	.028	-.062	.384**	-.190*	1
10. Quality of life	-.219*	.376**	.060	-.006	.094	-.113	-.569**	.292**	-.432**

*p<.05; **p<.01

Assumptions. The data were examined for any violations of assumptions required for multiple regression. Inspection of frequency distributions, histograms, Cook's Distance, and box plots yielded no outliers. Assumptions of normality, linearity, and homoscedasticity were visually assessed and confirmed using residual scatter plots. Normal distribution of the residuals was confirmed via q-q plots of predicted and observed values. Multicollinearity was assessed with tolerance and variance inflation factors, which were within normal limits.

Main Analyses

Research question 1. Parent history of psychopathology, elevated parent perceptions of stigma, and negative parent illness cognitions were expected to be related to increased parent reported anxiety features in youth with epilepsy. To test hypotheses 1a-1c, separate sequential multiple regression analyses were conducted. The *p*-value associated with the change in R^2 was examined at an alpha level of 0.017 (using the Bonferroni correction to adjust for multiple comparisons and a family-wise error rate of .05).

Hypothesis 1a. Parent history of psychopathology was expected to account for a significant amount of variance in parent reported child anxiety among pediatric epilepsy patients after controlling for gender, age, and IQ. Model statistics for all variables can be found in Table 5. IQ, gender, and age accounted for 5.3% of the variance in parent reported child anxiety, but none of the control variables contributed significantly to the overall model, $F(3, 113) = 2.132$, $p = .100$. When added to the model, parent history of

psychopathology accounted for 3.5% of the variance in parented reported child anxiety, but the change in R^2 did not reach statistical significance after controlling for multiple comparisons, *F* Change (1, 113) = 4.356, *p*=.039. The semipartial correlation of parent reported child anxiety with parent history of psychopathology was .187. This finding suggests that parent history of psychopathology did not contribute uniquely to the model.

Table 5: Parent history of psychopathology regression model.

	B	*SE B*	β	*p*	R^2	ΔR^2
Block 1	--	--	--	.100	.053	.053
Constant	42.301	5.165	--	.000	--	--
IQ	.105	.053	.182	.050	--	--
Age	-.001	.258	.000	.996	--	--
Gender	2.903	1.962	.135	.142	--	--
Block 2	--	--	--	.032	.088	.035
Constant	41.915	5.094	--	.000	--	--
IQ	.094	.053	.163	.076	--	--
Age	-.007	.254	-.002	.979	--	--
Gender	2.947	1.93	.137	.130	--	--
Parent Hx Psych	4.376	2.097	.188	.039	--	--

Note: *p*-value for Blocks 1 and 2 is the significance of the overall model F statistic

Hypothesis 1b. Parent perception of stigma was expected to account for a significant amount of variance in parent reported child anxiety among pediatric epilepsy patients after controlling for gender, age, and IQ. Model statistics for all variables can be found in Table 6. IQ, gender, and age accounted for 3.5% of the variance in parent reported child anxiety, but none of the control variables contributed significantly to the overall model, $F(3, 117) = 1.397$, $p = .247$. When added to the model, parent perception of stigma accounted for 5.6% of the variance in parented reported child anxiety, and the change in

R^2 was statistically significant, F Change (1, 116) = 7.153, p=.009. The semipartial correlation of parent reported child anxiety with parent perception of stigma was .237. This finding suggests that parent perceptions of stigma may uniquely contribute parent reported child anxiety features, even when demographic variables known to adversely impact child anxiety are taken into account. Parents who believe that their children are stigmatized due to their epilepsy also rate more features of anxiety in their children.

Table 6: Stigma regression model.

	B	*SE B*	β	*p*	R^2	ΔR^2
Block 1	--	--	--	.247	.035	.035
Constant	44.522	5.199	--	.000	--	--
IQ	.078	.053	.134	.146	--	--
Age	.040	.262	.014	.878	--	--
Gender	2.651	1.972	.122	.181	--	--
Block 2	--	--	--	.025	.091	.056
Constant	35.268	6.136	--	.000	--	--
IQ	.113	.053	.194	.037	--	--
Age	-.040	.257	-.014	.878	--	--
Gender	2.992	1.927	.138	.123	--	--
Stigma	3.000	1.122	.246	.009	--	--

Note: *p*-value for Blocks 1 and 2 is the significance of the overall model F statistic

Hypothesis 1c. Parent illness cognitions were expected to account for a significant amount of variance in parent reported child anxiety among pediatric epilepsy patients after controlling for gender, age, and IQ. Model statistics for all variables can be found in Table 7. IQ, gender, and age accounted for 3.5% of the variance in parent reported child anxiety, but none of the control variables contributed significantly to the overall model, $F(3, 117) = 1.397$, $p = .247$. When added to the model, parent illness cognitions accounted for 1.3% of the variance in parented reported child anxiety, but the change in R^2 did not reach

statistical significance after controlling for multiple comparisons, *F* Change (1, 116) = 1.612, *p*=.207. The semipartial correlation of parent reported child anxiety with parent illness cognitions was .114. This finding suggests that parent illness cognitions did not contribute uniquely to the model.

Table 7: Illness cognitions regression model.

	B	*SE B*	β	*p*	R^2	ΔR^2
Block 1	--	--	--	.247	.035	.035
Constant	44.522	5.199	--	.000	--	--
IQ	.078	.053	.134	.146	--	--
Age	.040	.262	.014	.877	--	--
Gender	2.651	1.972	.122	.181	--	--
Block 2	--	--	--	.220	.048	.013
Constant	56.981	11.098	--	.000	--	--
IQ	.076	.053	.130	.155	--	--
Age	.000	.263	.000	1.000	--	--
Gender	2.475	1.972	.114	.212	--	--
Illness cognitions	-.188	.148	-.116	.207	--	--

Note: *p*-value for Blocks 1 and 2 is the significance of the overall model F statistic

Research question 2. Parent perceptions of stigma and parent illness cognitions were expected to partially mediate the effect of parent history of psychopathology on parent reported anxiety features in youth with epilepsy. To test hypotheses 2a and 2b, mediations were assessed with a bias-corrected bootstrap confidence interval using the PROCESS macro (Hayes, 2013). The 95% bias-corrected bootstrap confidence intervals were examined, and if they did not include zero the indirect effect was considered statistically significant.

Hypothesis 2a. Parent perception of stigma was expected to mediate the relation between parent history of psychopathology and parent reported child anxiety after

controlling for gender, age, and IQ. The 95% bias-corrected bootstrap confidence interval of the indirect effect contained zero and was not significant (95% CI: -.6734 - 2.0633), see Table 8. This finding suggests that there is not a significant indirect effect of parent history of psychopathology on the BASC anxiety T-score through parent perceptions of stigma.

Table 8: Stigma mediation model.

	Effect	*SE**	*t*	*p*	*LLCI**	*ULCI**
Total effect	4.4317	2.2807	1.9431	.0546	-.0887	8.9520
Direct effect	3.9537	2.2220	1.7793	.0780	-.4507	8.3582
Indirect effect	.4780	.6674	--	--	-.6734	2.0633

**Indirect effect values show the bootstrapped SE and confidence intervals. LLCI=lower limit of CI; ULCI=upper limit of CI.*

Hypothesis 2b. Parent illness cognitions were expected to mediate the relation between parent history of psychopathology and parent reported child anxiety after controlling for gender, age, and IQ. The 95% bias-corrected bootstrap confidence interval of the indirect effect contained zero and was not significant (95% CI: -.2295 - .9254), see Table 9. This finding suggests that there is not a significant indirect effect of parent history of psychopathology on the BASC anxiety T-score through parent illness cognitions.

Table 9: Illness cognitions mediation model.

	Effect	*SE**	*t*	*p*	*LLCI**	*ULCI**
Total effect	4.4317	2.2807	1.9431	.0546	-.0887	8.9520
Direct effect	4.3905	2.2874	1.9194	.0576	-.1436	8.9245
Indirect effect	.0412	.2405	--	--	-.2295	.9254

** Indirect effect values show the bootstrapped SE and confidence intervals. LLCI=lower limit of CI; ULCI=upper limit of CI.*

Research question 3. Seizure severity was expected to moderate the possible effect of parent history of psychopathology on parent perceived stigma and on parent illness cognitions. To test hypotheses 2a and 2b, moderation was assessed with a simple moderation model using the PROCESS macro (Hayes, 2013). The 95% bias-corrected bootstrap confidence intervals were examined, and if they did not include zero the interaction was considered significant.

Hypothesis 3a. Seizure severity was expected to moderate the possible effect of parent history of psychopathology on parent perception of stigma after controlling for gender, age, and IQ. The 95% bias-corrected bootstrap confidence interval of the interaction contained zero and was not significant, p=.7091, see Table 10. This finding suggests that seizure severity does not moderate the relation between parent history of psychopathology and parent perception of stigma.

Table 10: Effect of parent history on stigma at varying levels of seizure severity.

	Effect/coeff	*SE*	*t*	*p*	*LLCI*	*ULCI*	R^{2**}
Interaction model	-.0304	.0812	-.3740	.7091	-.1914	.1306	.0011
Low severity	.2572	.2499	1.0292	.3057	-.2382	.7527	--
Medium severity	.1851	.1844	1.0036	.3178	-.1805	.5506	--
High severity	.1129	.2828	.3992	.6906	-.4478	.6735	--

*Low severity=2.5275; Medium severity=4.9035; High severity=7.2795
** R^2 is the increase in R^2 due to the interaction

Hypothesis 3b. Seizure severity was expected to moderate the possible effect of parent history of psychopathology on parent illness cognitions after controlling for gender, age, and IQ. The 95% bias-corrected bootstrap confidence interval of the interaction

contained zero and was not significant, p=.8047, see Table 11. This finding suggests that seizure severity does not moderate the relation between parent history of psychopathology and parent illness cognitions.

Table 11: Effect of parent history on illness cognitions at varying levels of seizure severity.

	Effect/coeff	*SE*	*t*	*p*	*LLCI*	*ULCI*	R^{2**}
Interaction model	-.1559	.6288	-.2479	.8047	-1.4024	1.0906	.0005
Low severity	-.2790	1.9354	-.1441	.8857	-4.1157	3.5577	--
Medium severity	-.6494	1.4278	-.4548	.6502	-3.4799	2.1811	--
High severity	-1.0199	2.1900	-.4657	.6424	-5.3612	3.3215	--

* Low severity=2.5275; Medium severity=4.9035; High severity=7.2795
** R^2 is the increase in R^2 due to the interaction

Additional analysis. To further understand the effects of stigma and seizure severity on parent reported anxiety, an additional post-hoc exploratory analysis was completed. Seizure severity was expected to moderate the effect of parent perceived stigma on parent reported child anxiety after controlling for gender, age, and IQ. The 95% bias-corrected bootstrap confidence interval of the interaction was significant, p=.0302, see Table 12. This finding suggests that there is an interaction between parent perceived stigma and seizure severity on parent reported child anxiety. As shown in Figure 7, at low levels of seizure severity (2.4045) there is not a significant relation between parent perceived stigma and parent reported child anxiety, p=.8062. However, at medium (4.8347) and high (7.2649) levels of seizure severity, there is a significant relation between parent perceptions of stigma and parent reported child anxiety (p=.0091 and p=.0008, respectively). This suggests that in parents of children with higher seizure severity, parents who believe their

child is stigmatized rate higher features of anxiety in their children, while parents of children with high seizure severity who perceive less stigma rate lower features of anxiety in their children. In parents of children with low seizure severity, parent perceptions of stigma are not related to their ratings of anxiety in their children.

Table 12: Effect of stigma on anxiety at varying levels of seizure severity.

	Effect/coeff	*SE*	*t*	*p*	*LLCI*	*ULCI*	R^{2**}
Interaction model	1.1119	.5066	2.1949	.0302	.1084	2.1154	.0368
Low severity	.4239	1.7237	.2460	.8062	-2.9906	3.8385	--
Medium severity	3.1260	1.1787	2.6520	.0091	.7909	5.4611	--
High severity	5.8280	1.6849	3.4590	.0008	2.4903	9.1657	--

*Low severity=2.4045; Medium severity=4.8347; High severity=7.2649
** R^2 is the increase in R^2 due to the interaction

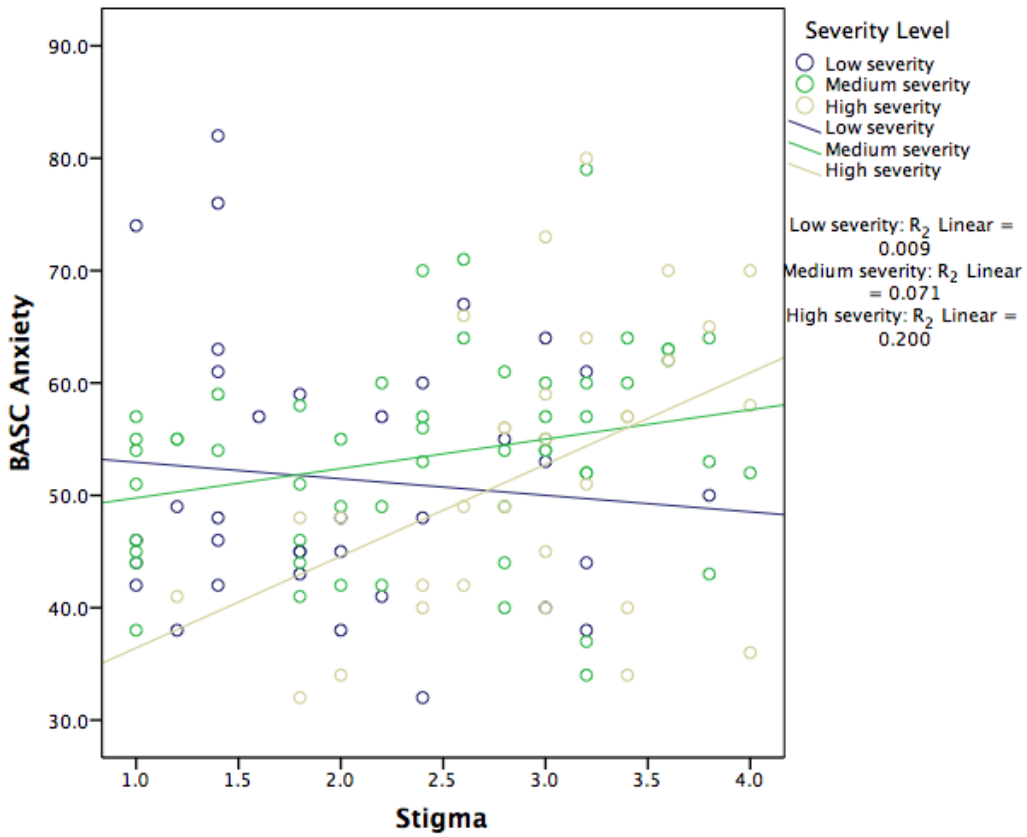

Figure 7: *Effect of stigma on anxiety at varying levels of seizure severity*. This figure represents the interaction between seizure severity and parent perceptions of stigma on parent reported child anxiety. The blue dots and line represent parent ratings of children with low seizure severity (ratings between 0 and 4; *n*= 35). The green dots and line represent parent ratings of children with medium seizure severity (ratings between 5 and 6; *n*= 55). The orange dots and line represent parent ratings of children with high seizure severity (ratings between 6 and 9; *n*= 31).

Research question 4. Seizure severity, parent reported anxiety, parent perceptions of stigma, and parent illness cognitions were expected to account for a significant amount of variance in HRQOL among youth with epilepsy after controlling for IQ. To test research question 4, a simultaneous multiple regression analysis was conducted. The *p*-value of the regression coefficient associated with the variable of interest was examined at an alpha

level of 0.05. The regression model was statistically significant, $F(5, 115) = 20.170$, $p = .000$, and accounted for 46.7% of the variance in parent reported quality of life ($R^2 = 0.467$, adj $R^2 = 0.444$). Model statistics for all predictor variables can be found in Table 13. These results indicate that that stigma, parent illness cognitions, and parent reported child anxiety all uniquely contribute to HRQOL, even when IQ and seizure severity are taken into account.

Table 13: Health-related quality of life regression model.

	B	*SE B*	β	*p*	R^2
Overall model	--	--	--	.000**	.467
Constant	56.539	14.574	--	.000**	--
IQ	.223	.062	.264	.001**	--
Seizure severity	-1.163	.492	-.180	.020*	--
Stigma	-6.512	1.381	-.367	.000**	--
Illness cognitions	.366	.168	.155	.032*	--
Anxiety	-.236	.103	-.163	.023*	--

*p<.05; **p<.01

Additional analysis. To further understand the role of these variables on HRQOL, additional exploratory simultaneous multiple regression analyses were completed for each subscale of the QOLCE-55.

Cognitive. The regression model for the cognitive domain was statistically significant, $F(5, 115) = 5.487$, $p = .000$, and accounted for 19.3% of the variance in parent reported quality of life in the cognitive domain ($R^2 = .193$, adj $R^2 = .158$). Model statistics can be found in Table 14. These results indicate that parent reported child anxiety contributes to parent reported quality of life in the cognitive domain, even after accounting

for the child's IQ. Parents who reported higher levels of child anxiety reported lower quality of life in the cognitive domain for their child.

Table 14: Health-related quality of life cognitive domain regression model

	B	*SE B*	β	*p*	R^2
Cognitive domain model	--	--	--	.000**	.193
Constant	23.753	23.110	--	.306	--
IQ	.405	.099	.372	.000**	--
Seizure severity	.262	.781	.032	.738	--
Stigma	-2.396	2.189	-.105	.276	--
Illness cognitions	.265	.267	.087	.324	--
Anxiety	-.334	.163	-.179	.043*	--

*p<.05; **p<.01

Emotional. The regression model for the emotional domain was statistically significant, $F(5, 115) = 10.694$, $p = .000$, and accounted for 31.7% of the variance in parent reported quality of life in the emotional domain ($R^2 = .317$, adj $R^2 = .288$). Model statistics can be found in Table 15. These results indicate that parent perceptions of stigma and parent illness cognitions contribute to parent reported quality of life in the emotional domain, even after accounting for parent reported child anxiety and intelligence. Parents who reported higher perceptions of stigma and more negative illness cognitions reported lower quality of life in the emotional domain for their child.

Table 15: Health-related quality of life emotional domain regression model

	B	*SE B*	β	*p*	R^2
Emotional domain model	--	--	--	.000**	.317
Constant	61.801	13.599	--	.000**	--
IQ	.116	.058	.166	.049*	--
Seizure severity	.063	.459	.012	.891	--
Stigma	-4.093	1.288	-.280	.002**	--
Illness cognitions	.463	.157	.239	.004**	--
Anxiety	-.325	.096	-.271	.001**	--

*p<.05; **p<.01

Social. The regression model for the social domain was statistically significant, $F(5, 115) = 17.095$, $p = .000$, and accounted for 42.6% of the variance in parent reported quality of life in the social domain ($R^2 = .426$, adj $R^2 = .401$). Model statistics can be found in Table 16. These results indicate that parent perceptions of stigma and seizure severity contribute to parent reported quality of life in the social domain. Parents who reported higher perceptions of stigma reported lower quality of life in the social domain for their child.

Table 16: Health-related quality of life social domain regression model

	B	*SE B*	β	*p*	R^2
Social domain model	--	--	--	.000**	.434
Constant	105.785	23.889	--	.000**	--
IQ	.121	.102	.091	.238	--
Seizure severity	-3.361	.807	-.330	.000**	--
Stigma	-9.735	2.263	-.348	.000**	--
Illness cognitions	.274	.276	.074	.322	--
Anxiety	-.329	.169	-.143	.054	--

*p<.05; **p<.01

Physical. The regression model for the physical domain was statistically significant, $F(5, 115) = 14.712$, $p = .000$, and accounted for 39% of the variance in parent

reported quality of life in the physical domain ($R^2 = .390$, adj $R^2 = .364$). Model statistics can be found in Table 17. These results indicate that intelligence, parent perceptions of stigma, and seizure severity all contribute to parent reported quality of life in the physical domain. Parents reported lower quality of life in the social domain if their child had a lower IQ, more severe seizures, or if the parent reported higher perceptions of stigma.

Table 17: Health-related quality of life physical domain regression model

	B	*SE B*	β	*p*	R^2
Physical domain model	--	--	--	.000**	.390
Constant	31.684	22.137	--	.155	--
IQ	.261	.095	.217	.007**	--
Seizure severity	-1.521	.748	-.166	.044*	--
Stigma	-9.791	2.097	-.389	.000**	--
Illness cognitions	.481	.256	.144	.063	--
Anxiety	.050	.156	.024	.748	--

*p<.05; **p<.01

Summary

Research question 1 examined the extent that parent factors influenced parent reported anxiety in youth with epilepsy. Findings suggested that parent illness cognitions and parent history of psychopathology did not predict parent reported child anxiety after controlling for gender, age, and IQ. However, parents who believed their children experienced more stigma related to their epilepsy rated higher anxiety in their children.

Research question 2 examined whether parent factors mediated the possible effect of parent history of psychopathology on parent reported anxiety in youth with epilepsy. Parent perceptions of stigma and parent illness cognitions did not mediate the relation between parent history of psychopathology and parent reported child anxiety.

Research question 3 examined the extent that seizure severity interacted with parent factors to influence parent reported anxiety in youth with epilepsy. Seizure severity did not moderate the relation between parent history of psychopathology and parent perception of stigma and seizure severity did not moderate the relation between parent history of psychopathology and parent illness cognitions. Additional analysis revealed a statistically significant interaction between parent perceptions of stigma and seizure severity. Seizure severity moderated the relation between parent perceptions of stigma and parent reported child anxiety. At lower levels of seizure severity, there was not a significant relation between parent perceptions of stigma and parent reported child anxiety. However, at higher levels of seizure severity, parents who believed their children experienced more stigma related to their epilepsy also rated higher anxiety in their children.

Research question 4 examined how family factors, parent reported anxiety, and seizure severity influenced quality of life in youth with epilepsy. Results indicated that intelligence, seizure severity, parent reported anxiety, parent perceptions of stigma, and parent illness cognitions were all statistically significant predictors of HRQOL. See Table 18 for a summary of which variables were statistically significant for each domain.

Table 18: Summary of quality of life findings by domain

	Cognitive	Emotional	Social	Physical
IQ	++	+	-	++
Seizure severity	-	-	++	+
Stigma	-	++	++	++
Illness cognitions	-	++	-	-
Anxiety	+	++	-	-

+p<.05; ++p<.01; - p>.05

Chapter 5: Discussion

Summary

Compared to children with other chronic health conditions, youth with epilepsy are considered to be at the highest risk for anxiety symptoms (Pinquart & Shen, 2011), and yet, research regarding risk and protective factors for anxiety in youth with epilepsy is sparse. The purpose of this study was to examine parent reported anxiety in pediatric epilepsy and the role of seizure severity, parent history of psychopathology, parent illness cognitions, and parent perceptions of stigma as well as the impact of these variables on Health-Related Quality of Life (HRQOL). Analyses consisted of a series of sequential and simultaneous multiple regressions and tests of mediation and moderation using the Hayes (2013) PROCESS Macro in SPSS version 22.0.

Anxiety. In this sample of referred youth with epilepsy, parent reported anxiety, as measured by the BASC parent report, was in the average range (mean 52.60; SD 10.77). Additionally, over 25% of parents reported child anxiety symptoms in the at-risk (17.4%) or clinically significant (8.3%) range. These results are consistent with rates reported in other samples of youth with epilepsy (e.g., Titus et al., 2008; Williams et al., 2003) and in a recent meta-analysis of adults with epilepsy (Scott et al., 2017). It is important to note that this study relied upon one time parent report of child anxiety. Parents may under-indentify internalizing problems in children and use of diagnostic interview (e.g., Jones et al., 2007) has demonstrated higher rates of anxiety in this population. Despite these

limitations, this study contributes to research characterizing the rates of parent reported anxiety in youth with epilepsy and confirms the need to further understand the risks and protective factors involved in the development and maintenance of anxiety in pediatric epilepsy.

Parent history of psychopathology. In the literature, parent history of psychopathology is associated with higher risk for anxiety in the general population (e.g., Micco et al., 2009) and in the context of pediatric epilepsy (e.g., Jones et al., 2015; Schraegle & Titus, 2017a). In the current study, after adjusting for multiple comparisons, parent history of psychopathology did not explain a significant amount of variance in parent reported child anxiety. This result is unexpected, but it is likely attributable to limitations in study design. The use of a dichotomous variable and the lower percentage of parents who reported a history of psychopathology (29%) likely contributed to smaller power to detect differences than originally calculated in the power analysis.

Parent perceptions of stigma. Stigma has been an overarching hypothesis for understanding the psychosocial reasons for higher rates of anxiety in the epilepsy population in comparison to healthy controls and comparable groups with chronic health conditions (Davies et al., 2003; Hermann et al., 1988). This study replicates previous findings (Austin, MacLeod, Dunn, Shen, & Perkins, 2004; Austin et al., 2014; Adewuya & Ola, 2005) and demonstrates that parents who rated higher perceptions of stigma reported more features of anxiety in their child. This suggests that children who are stigmatized are more likely to be anxious. Parent perceptions of stigma accounted for

approximately 5.6% of the variance in parent reported child anxiety, and stigma may play a small, but important role in the development and maintenance of anxiety in pediatric epilepsy.

Parent perceptions of stigma may also relate to parent reported child anxiety indirectly. Perhaps parents who have more perceptions of stigma may also have reduced perceptions of control. Chorpito and Barlow (1998) suggest that individuals can develop a psychological vulnerability for anxiety when they perceive events to be outside of their control after experiencing uncontrollable events (e.g., seizures). Field and Purkis (2011) theorize that children can acquire fear through verbal information or observations of others. If parents who perceive high levels of stigma inadvertently model their child's epilepsy to be outside of their control, their children may perceive lower levels of control. Previous research has demonstrated that individuals who perceive lower levels of control report higher symptoms of anxiety (Gallagher et al., 2014).

Parent perceptions of stigma may also relate to certain parenting behaviors that are associated with higher anxiety, such as overprotectiveness and accommodation (Anthony et al., 2003). Previous research has found that higher rates of child anxiety were reported when parents granted less autonomy to their child (McLeod et al., 2007). Parents who perceive more stigma may engage in more overprotective parenting to limit their child's exposure to this perceived stigmatizing environment. Parents with higher ratings of perceived stigma may also contribute to their child's anxiety by socializing them to the dangers (e.g., stigma) of the outside world (Murray et al., 2009). Parents with higher rates

of perceived stigma may also be more likely to accommodate their child's anxiety by allowing them to avoid anxiety provoking situations. Because this study measured parent perceptions of stigma, and did not directly measure parenting behaviors, more research is needed to elucidate the connection between parenting behaviors and perceptions of stigma.

It is also important to consider alternate hypotheses for the relation between parent perceptions of stigma and parent reported child anxiety. In this model, it was assumed that parent perceptions of stigma preceded symptoms of parent reported child anxiety. However, previous research demonstrates the bidirectional relationship of anxiety and epilepsy, in that anxiety symptoms may precede epilepsy diagnosis (N. C. Jones et al., 2008). Therefore, it is also likely that in some cases, parent reported child anxiety symptoms preceded the epilepsy diagnosis and thus also preceded parent formation of perceptions of stigma. In these scenarios, parent perceptions of stigma may maintain or exacerbate parent reported anxiety symptoms. While the questions on the epilepsy stigma scale are placed in the context of epilepsy, parents of youth with epilepsy and anxiety may also be more likely to perceive higher levels of stigma. Furthermore, parents who rate higher perceptions of stigma may also be more inclined to rate their child's anxiety as more severe. It may be difficult to disentangle parent reported perceptions of stigma with parent reported child anxiety, and future research should collect anxiety and stigma ratings through different sources (e.g., child, teacher) and methods (e.g., diagnostic interview, observation).

Parent perceptions of stigma were also hypothesized to mediate the relation between parent history of psychopathology and parent reported child anxiety. However, this study did not find a statistically significant indirect effect; this is likely attributable to the smaller sample of parents with a history of psychopathology than originally anticipated. Additionally, this study used parent history of psychopathology, and not current levels of psychopathology or distress. Future research should measure current levels of parent psychopathology or distress.

Parent illness cognitions. It was hypothesized that more negative parent illness cognitions would be associated with higher parent reported anxiety symptoms. This current research did not support this hypothesis. This result was unexpected because previous research demonstrates that negative illness cognitions regarding a child's illness is related to parent distress, which, in turn, is related to more emotional distress in children (Colletti et al., 2008; Nicolaas et al., 2016; Robinson et al., 2007; Steele et al., 2004). While the Illness Cognitions Questionnaire measures an aspect of a parent's coping and adjustment to their child's illness, illness cognitions are just one component of coping. Future research may wish to examine other aspects of parent coping and explore the relation between parent illness cognitions or coping and parenting behaviors.

It was also hypothesized that parent illness cognitions would mediate the relation between parent history of psychopathology and parent reported child anxiety. However, this study did not find a statistically significant indirect effect. This is likely attributable to

the previous finding that parent illness cognitions were not associated with higher parent reported anxiety symptoms.

Seizure severity. Epilepsy variables have been consistently explored as possible causes of higher rates of anxiety in pediatric epilepsy. In this study, seizure severity was examined as a variable that may interact with other psychosocial variables. It was hypothesized that seizure severity would moderate the effect of parent history of psychopathology on parent perceived stigma (i.e., in the context of low seizure severity, parents with a history of psychopathology would report higher levels of perceived stigma, but in the context of high seizure severity, both parents with and without a history of psychopathology would report high levels of perceived stigma (see Figure 3)). A similar interaction was hypothesized for parent illness cognitions, in that seizure severity would moderate the effect of parent history of psychopathology on parent illness cognitions (see Figure 4). In both models, there was no interaction between parent history of psychopathology and seizure severity.

This finding suggests that the relation between parent history of psychopathology and parent illness cognitions and parent perceptions of stigma is not dependent on seizure severity. While an interaction was hypothesized, this finding is not completely unexpected because moderation effects are rare (Keith, 2014). This study may not have been adequately powered to detect a moderation effect when using a dichotomous variable for parent history of psychopathology. Additionally, parent illness cognitions and parent perceptions of stigma may be more dependent upon current levels of parent distress, and

not history of psychopathology. Future research should examine the effect of seizure severity on parent perceptions of stigma and illness cognitions in the context of current parent distress due to its relation to emotional distress in the child (Colletti et al., 2008; Nicolaas et al., 2016; Robinson et al., 2007; Steele et al., 2004).

To further explore the effect of seizure severity on parent perceptions of stigma and parent reported child anxiety, a post hoc exploratory analysis was completed. Seizure severity was hypothesized to moderate the relation between parent perceptions of stigma and parent reported child anxiety. Results demonstrated that there was an interaction between parent perceptions of stigma and seizure severity on parent reported child anxiety (see Figure 7). This finding suggests that there is a conditional effect of parent perceptions of stigma on parent reported child anxiety at varying levels of seizure severity. In other words, at low levels of seizure severity, there was not a relation between parent perceptions of stigma and parent reported child anxiety. However, at higher levels of seizure severity, parents with more perceptions of stigma also reported higher levels of child anxiety.

There are several reasons why this interaction between seizure severity and parent perceptions of stigma may occur. First, in the literature it has been demonstrated that higher seizure severity is associated with higher perceptions of stigma (Austin et al., 2014). Epilepsy is more visible in children with more severe seizures, and perhaps perceptions of stigma may be more internalized in these youth. Youth with greater seizure severity may be more susceptible to experiencing stigma related to their epilepsy, and therefore are more likely to develop anxiety. The importance of the context of high seizure severity is

supported by Gandy et al. (2012), who hypothesized that stigma might be more important in individuals with poorly controlled epilepsy, while stigma is less important for individuals with epilepsy who have less frequent seizures.

The interaction between parent perceptions of stigma and seizure severity may also indirectly affect parent reported anxiety through parenting behaviors. Parents who perceive high stigma may engage in more over-protective parenting, particularly when their child's seizures are more severe. In contrast, low parent perceptions of stigma in parents of children with high seizure severity may be a protective factor for children. These parents with lower perceptions of stigma may model higher perceptions of control and may not be as over-protective. In contrast, parents of children with lower seizure severity may not need to engage in as much over-protective parenting. More research is needed to determine if parenting behaviors change in the context of higher seizure severity along varying levels of perceived stigma.

It is also important to consider alternate hypotheses and note that perceptions of stigma and child anxiety were measured through parent report. Perhaps parents with children with more severe epilepsy rated more perceived stigma when their child had symptoms of anxiety. Alternatively, parents of children with high seizure severity who rated higher perceived stigma may also be more likely to rate more features of anxiety. Furthermore, perhaps in the context of lower levels of seizure severity, parents may not perceive as much stigma towards their child's epilepsy, and therefore there is not enough variability in stigma to predict parent reported child anxiety. However, in the context of

high seizure severity, there is more variability in parent perceptions of stigma, and higher perceived stigma is related to higher parent reported child anxiety.

Quality of life. It is important to consider the impact of family and psychosocial factors on quality of life in youth with epilepsy. Intelligence, seizure severity, stigma, parent illness cognitions, and parent reported child anxiety all predicted parent reported health related quality of life. Additionally, all of the examined variables affected quality of life differentially across the various domains, see Table 18.

As demonstrated in previous research, parent reported anxiety is related to lower quality of life in youth with epilepsy (Baca et al., 2011; Loiselle et al., 2016; Puka & Smith, 2015; Stevanovic et al., 2011). Not surprisingly, lower parent reported anxiety symptoms were related to better quality of life in the emotional domain. Many questions in the emotional domain relate to symptoms of anxiety (e.g., worry) and depression, so there is some construct overlap within this domain. However, parent reported anxiety was also an important predictor of health-related quality of life in the cognitive domain, even after accounting for the child's IQ. A recent meta-analysis suggests that anxiety impacts cognitive functioning, particularly working memory (Moran, 2016). This research demonstrates the need to address anxiety in order to improve a child's quality of life.

Parent perception of stigma was an important predictor of total health related quality of life, as well as quality of life in the emotional, social, and physical domains. In the emotional domain, parents who perceived their child as more stigmatized because of their epilepsy reported poorer quality of life in areas such as feeling valued and understood.

Parent perception of stigma was also an important predictor of quality of life in the social domain. The social domain also captures certain aspects of stigma, such as feelings of isolation and frightening others, which may demonstrate some construct overlap. However, children with epilepsy may also have difficulty participating in social activities (Institute of Medicine, 2012) and this may be compounded when they are also experiencing stigma. Finally, parent perception of stigma was a significant predictor of quality of life in the physical domain. Parents with more perceptions of stigma may engage in more overprotective parenting, such as limiting or restricting their child's physical activities or social interactions.

Parent illness cognitions were a significant predictor of overall quality of life and more positive parent illness cognitions were related to improved quality of life in the emotional domain. Interestingly, parent illness cognitions were related to emotional quality of life, but not parent reported child anxiety. Perhaps parent illness cognitions are related to broader aspects of emotional functioning captured on the quality of life measure, such as depression and oppositional behaviors.

It is noteworthy that seizure severity was only a significant predictor of quality of life in the physical and social domains. This aligns with other research in pediatric epilepsy and research on outcomes of epilepsy surgery that demonstrate that seizure outcomes are only significant predictors of quality of life in the physical and social domains (Conway, Widjaja, & Smith, 2018; Schraegle & Titus, 2016; Titus et al., 2013). This suggests that while improving seizure outcomes is important, other psychosocial factors, such as anxiety,

cognitive functioning, parent illness cognitions, and parent perceptions of stigma, need to be addressed in order to improve quality of life in youth with epilepsy. Taken together, these findings suggest the multitude of psychosocial factors that are important to quality of life in youth with epilepsy.

Limitations

While this research demonstrates the importance of parent factors on parent reported child anxiety in youth with epilepsy, there are also several limitations to consider. First, it is important to note the limited generalizability of these findings as well as the representativeness of this sample for the epilepsy population. This research was conducted with a clinically referred group of youth with epilepsy. These patients were under consideration for epilepsy surgery and/or demonstrated a need for a neuropsychological evaluation. Therefore, these patients may represent a sample of youth with more severe epilepsy. Additionally, while this research controlled for the effects of intelligence, this sample of youth had a lower mean IQ (78) than the mean IQ (84.96) reported in a recent population-based sample of youth with epilepsy (Reilly, Atkinson, Das, et al., 2015a). The results of this paper should be considered in the context of this more severe patient population and may not be representative of the overall epilepsy community.

As discussed previously, this research relied upon a dichotomous variable for parent history of psychopathology. The use of a dichotomous variable limits the power of understanding the effects of parent psychopathology on child outcomes. Additionally, this

variable was based off of parent report, which might be prone to social desirability bias. Finally, while use of history of psychopathology may be useful in understanding the genetic component of anxiety, current psychopathology or parent distress would be more helpful in understanding how current emotional distress in the parent affects child outcomes.

It is also important to consider that this study relied upon the use of parent reported measures of anxiety. Research demonstrates that parents under-report internalizing psychopathology and that parent and child ratings are only modestly correlated (Achenbach, McConaughy, & Howell, 1987). This suggests that both parent and child ratings may need to be considered in order to more fully understand the emotional state of the child. Furthermore, this research relied upon measures of parent perceptions of various constructs and not direct measures of parent behaviors. It is unclear whether parent perceptions of stigma and parent illness cognitions are directly related to parenting behaviors, such as overprotectiveness and accommodation.

Additionally, this research is cross-sectional in nature, limiting the understanding of temporal precedence. It has been hypothesized that epilepsy and anxiety have a bidirectional relationship and as mentioned previously, symptoms of anxiety may precede the diagnosis of epilepsy. This study is also limited by the fact that it did not include a control group comparison.

Finally, while it was helpful to represent seizure severity as one variable, this also limits the interpretation of results (e.g., a score of a 5 could represent a child on

monotherapy who has daily absence seizures or a child on monotherapy with yearly generalized tonic-clonic seizures). The use of one variable makes it difficult to interpret results and make recommendations. Additionally, some constructs, such as age of onset and intractability status, were not used in the seizure severity variable. Difficulty quantifying seizure severity is an ongoing issue within epilepsy research, and more effort is needed to fully understand the best way to conceptualize this construct.

Recommendations for research

Future research should address the identified limitations in this study's design. Use of a longitudinal analysis in a larger community-based sample might be helpful to elucidate the temporal precedence of risk and protective factors for anxiety in pediatric epilepsy. A population-based sample would allow for findings that can be generalized to the general epilepsy population and use of a larger sample size would also allow stratification based on variables known to be associated with anxiety, including age, gender, and IQ.

There are also several ways limitations in measurement may also be addressed. In this study, anxiety was measures through the use of the BASC parent report. The BASC is typically a screening tool, so it would be important to use well-validated ratings of anxiety (e.g., MASC) or semi-structured interviews (e.g., K-SADS) in future research. Use of multiple informants (e.g., parent, child, clinician) across all measures would demonstrate whether these findings are similar across different contexts. Additionally, it would be beneficial to obtain direct measures of parenting behaviors (e.g., overprotectiveness, accommodation) and psychopathology/emotional distress to further elucidate whether

parent perceptions of stigma are directly related to parent behaviors or parent psychopathology/ emotional distress. Finally, more research is needed to determine the best way to quantify seizure severity and which seizure-related variables affect psychosocial outcomes.

More research is needed to understand what factors are related to an increased risk for anxiety and stigma in order to create modifiable targets for intervention. It would be interesting to conduct research that may determine whether interventions that help alleviate perceptions of stigma (e.g., psychoeducation) could reduce anxiety symptoms in youth with epilepsy. Alternatively, research examining whether treatment of anxiety can lead to reduced perceptions of stigma may also be beneficial. Use of longitudinal research may elucidate the temporal precedence of these variables.

While parent illness cognitions were not predictors of parent reported child anxiety in this study, more research may be needed to demonstrate whether parent illness cognitions play a role in anxiety in youth with epilepsy. Preliminary evidence from the emotional domain of health-related quality of life suggests that parent illness cognitions may be related to other aspects of emotional functioning in the child, such as depression or behavior difficulties. Future research could use different ways to measure parent coping or explore the relation between parent and child illness cognitions with other aspects of psychosocial functioning.

Finally, future research should focus on the relation between parenting behaviors and child anxiety in epilepsy. While parents may model or verbalize their cognitions and

perceptions, parent behaviors, such as over-protectiveness and accommodation, are related to child anxiety and can be modifiable targets for intervention. Parents of children with epilepsy could be compared to parents of children with other chronic health conditions to determine if there are differences in over-protectiveness or limitation of their child's activities.

Implications for clinical practice

Neuropsychologists and other clinicians working with youth with epilepsy should be aware of the higher rates of anxiety within this population and implement screening procedures to ensure youth with epilepsy are receiving adequate services. Other studies highlight the lack of children with epilepsy receiving intervention for mental health needs (Caplan et al., 2005) and clinicians should work to provide appropriate referrals. Cognitive behavioral therapy, particularly the use of exposure therapy, in combination with medication management is the ideal treatment for anxiety (Walkup et al., 2008). Clinicians working with youth with epilepsy who are experiencing anxiety should be aware of the unique context of epilepsy when delivering intervention. The unpredictable nature of seizures as well as the social stigma of having seizures may be important targets for intervention.

Parents may also be an important target for intervention. This current research suggests that parent perceptions of stigma may play an important role in the development or maintenance of anxiety. Clinicians may want to work with parents to understand how these perceptions of stigma may influence how parents interact with and maintain their

child's anxiety. These perceptions of stigma may be particularly important in the context of more severe epilepsy. Alternatively, if high levels of perceived stigma and high levels of parent reported child anxiety are artifacts of parent distress and over-reporting, parents who report high levels of perceived stigma may over-report anxiety symptoms in their child. Parent reported measures may need to be interpreted in the context of high perceptions of stigma and high seizure severity.

Finally, it is important for clinicians working with youth with epilepsy and their families to understand the impact anxiety and other parent factors may have on quality of life. While seizure severity is generally the target of intervention in pediatric epilepsy (and is an important aspect of overall quality of life and quality of life in the physical and social domains) there are other psychosocial variables that impact quality of life. Parent reported symptoms of anxiety are important predictors of quality of life in the cognitive and emotional domains and stigma was an important predictor of quality of life across the social, emotional, and physical domains. This suggests that stigma and anxiety may be important targets of intervention that can lead to improved quality of life in youth with epilepsy.

Conclusion

The development of anxiety in pediatric epilepsy is multifactorial, and can be driven by biological, psychosocial, and environmental factors. The importance of family factors in the development and maintenance of anxiety is a burgeoning area of research in pediatric epilepsy. This current work demonstrates the potential for parent perceptions of

stigma to play an important role in parent reported anxiety in pediatric epilepsy, particularly in the context of high seizure severity. More research is needed to understand the temporal precedence of this relationship (e.g., do parent perceptions of stigma influence child anxiety, or are more stigmatized perceptions formed in the context of child anxiety?). Individuals working with youth with epilepsy should be aware of the high rates of parent reported anxiety and potential role of stigmatization in the development or maintenance of anxiety.

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